DESIGN AND SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS WITH SULPHUR AND NITROGEN CONTAINING HETEROCYCLES AND RELATED COMPOUNDS

RESUME

THESIS

SUBMITTED FOR THE DEGREE OF

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IN

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BY

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FACULTY OF SCIENCE
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RESUME

The thesis describes the work related to synthesis, structure elucidation, stereochemistry and biological assay grouped in six chapters as Chapter-1 (2,2-disubstituted-thiazolidin-4-ones), Chapter-2 (3,5-disubstituted-2-pyrazolinyl-thiocarboxamides), Chapter-3 (2-[3,5-disubstituted-2-pyrazolinyl]thiazolin-4-ones), Chapter-4 (1,3,3-tris(*p*-chlorophenyl) propene), Chapter-5 (4'-chloroflavone) and Chapter-6 (Biological screening : study for anticancer and antibacterial activity).

The techniques used for structure elucidation are ^{1}H-NMR, ^{13}C-NMR, DEPT, 2-DNMR (COSY, HETCOR, Long-range HETCOR) including DCI-MS, EI-MS, FAB-MS, HRMS, IR and FTIR.

CHAPTER - 1

2,2-Disubstituted-Thiazolidin-4-ones from α,β-Unsaturated Enones

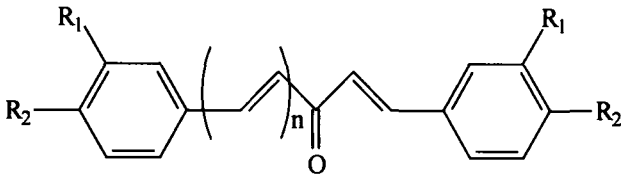
In recent years, it has been found that the interest in thiazolidin-4-ones for medical application is increasing strongly. The thiazolidin-4-ones, their derivatives and analogues have exhibited unusually high *in vitro* activity against *Mycobacterium tuberculosis*, highly potent and selective anti-Platelet Activiting Factor activity and broad spectrum activity against various diseases. Because thiazolidin-4-ones were proven to be highly potent and selective and as part of our aim in search of biologically active compounds with sulphur and nitrogen containing heterocycles, we have undertaken the synthesis of these *four novel compounds*, ***2-[2,2-bis(4-chlorophenyl)ethyl]-2-(4-chlorophenyl)thiazolidin-4-one (3), 2,2-di[2-(4-chlorophenyl)-2-(3,4-dimethoxyphenyl)ethyl]thiazolidin-4-one (6), 2,2-di[2-(4-chlorophenyl)-2-3,4-dimethoxyphenyl)ethyl]-5-(methyl)thiazolidin-4-one (7) and 2,2-***

di[2,2-bis(4-chlorophenyl)ethyl]-5-(methyl)thiazolidin-4-one (10). The compound **(3)** has been obtained from 4,4'-dichlorochalcone **(1)** via 1,3,3-tris(4-chlorophenyl)propan-1-one **(2)** using mercaptoacetic acid. Compound **(6)** and **(7)** both from 1,5-bis(3,4-dimethoxyphenyl)pent-1,4-dien-3-one **(4)** via 1,5-bis(4-chlorophenyl)-1,5-bis(3,4-dimethoxyphenyl)pentan-3-one **(5)** using mercapto acetic acid in the former and α-mercaptopropionic acid in the latter and the compound **(10)** from 1,5-bis(4-chlorphenyl)pent-1-4-dien-3-one **(8)** via 1,1,5,5-tetra(4-chlorophenyl)pentan-3-one **(9)** using α-mercaptopropionic acid, all in the presence of ammonium carbonate as a source of ammonia **(SCHEME-I)**.

The synthesis of target compounds **(3)**, **(6)**, **(7)** and **(10)** were performed in two steps **(SCHEME-I)**.

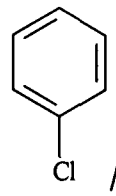
(i) The adducts **(2)**, **(5)** and **(9)** were first prepared by the reaction of the corresponding enones **(1)**, **(4)** and **(8)** with dry chlorobenzene in the presence of anhydrous aluminium chloride at room temperature, in good yields.

(ii) The adducts **(2)**, **(5)** and **(9)** were then condensed with α-mercaptoalkanoic acids and ammonium carbonate furnished four novel compounds, 2-[2,2-bis(4-chlorophenyl) ethyl]-2-(4-chlorophenyl) thiazolidin -4-one **(3)**, 2,2-di[2-(4-chlorophenyl)-2-(3,4-dimethoxyphenyl)ethyl] thiazolidin-4-one **(6)**, 2,2-di[2-(4-chlorophenyl-2-(3-4-dimethoxyphenyl)ethyl]-5-(methyl) thiazlidin-4-one **(7)** and 2,2-di[2,2-bis(4-chlorophenl) ethyl]-5-(methyl) thiazolidin-4-one **(10)**.

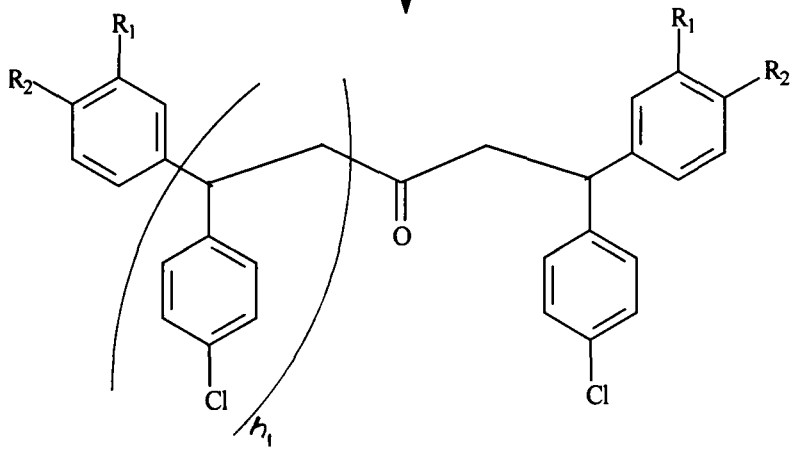


1) $R_1 = H, R_2 = Cl, \quad n = 0$
4) $R_1 = R_2 = OMe, \quad n = 1$
8) $R_1 = H, R_2 = Cl, \quad n = 1$

Step 1



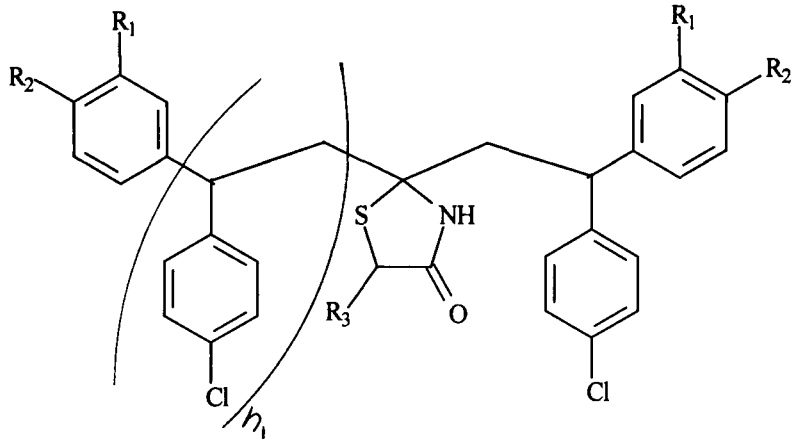
anhyd.$AlCl_3$ (molar ratio, 1: large excess[122] : 3), stirred at r.t., 3-8 h.



2) $R_1 = H, R_2 = Cl, \quad n_1 = 0$
5) $R_1 = R_2 = OMe, \quad n_1 = 1$
9) $R_1 = H, R_2 = Cl, \quad n_1 = 1$

Step 2

R_3—CH(SH).COOH/$(NH_4)_2CO_3$ (molar ratio, 1:1.30:5.25), dry benzene, reflux, 40-45h.
(R_3 = H, mercaptoacetic acid or thioglycollic acid
$R_3 = CH_3$, α-mercaptopropionic acid)



3) $R_1 = H, R_2 = Cl, R_3 = H \quad n_1 = 0$
6) $R_1 = R_2 = OMe, R_3 = H \quad n_1 = 1$
7) $R_1 = R_2 = OMe, R_3 = Me \quad n_1 = 1$
10) $R_1 = H, R_2 = Cl, R_3 = Me \quad n_1 = 1$

SCHEME-I

The structures / stereochemistry of compound **(3)** **(FIG. 1)** was established on the basis of spectral studies such as IR, DCI-MS, HRMS, ^{1}H-NMR, ^{13}C-NMR, NOE-experiments, COSY, HETCOR and Long-range HETCOR.

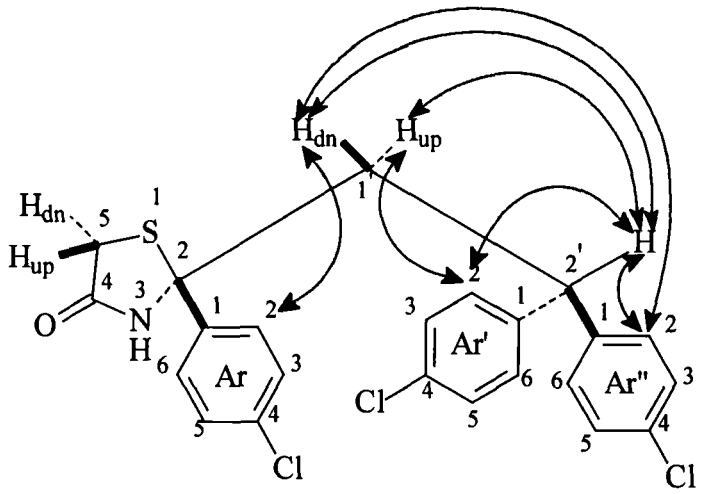


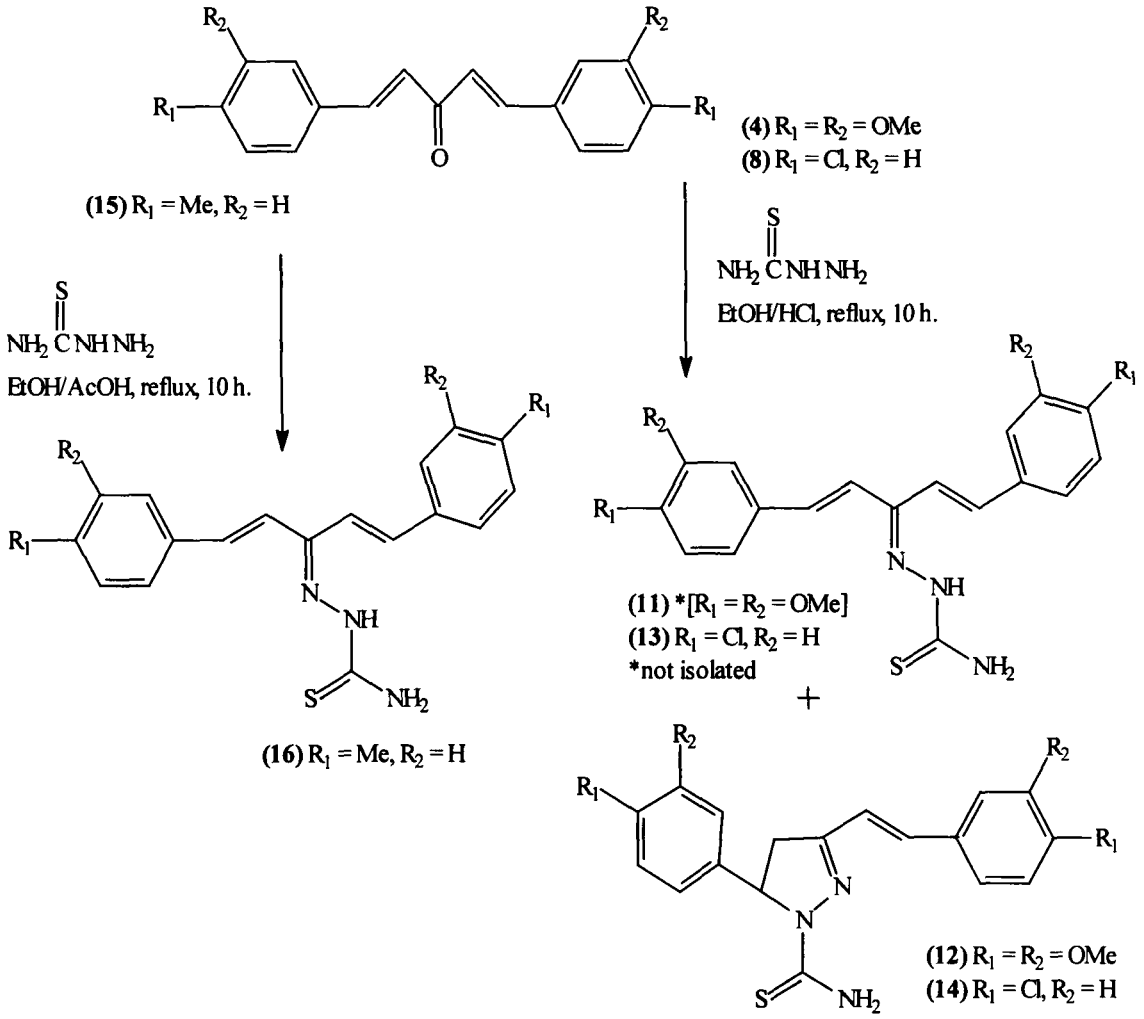
FIG. - 1

CHAPTER - 2

3,5-Disubstituted-2-pyrazolinyl-Thiacarboxamides from Dienones

Pyrazoline derivatives are associated with a wide range of biological activities such as antibacterial, antifungal, antiinflammatory, analgesic, antitumor and anti-HIV activity. Keeping in view of the clinical importance of pyrazolines and as part of our work in search of biologically active sulphur and nitrogen containing heterocycles, here we report the synthesis of 3,5-disubstituted-2-pyrazolinyl-thiocarboxamides **(12)** and **(14)** from dienones **(4)** and **(8)** using thiosemicarbazide in ethanol **(SCHEME-III)**.

It consists of the reactions of dienones, 1,5-bis(3,4-dimethoxyphenyl)pent-1,4-dien-3-one **(4)** and 1,5-bis(4-chlorophenyl) pent-1,4-dien-3-one **(8)** with thiosemicarbazide in the presence of hydrochloric



SCHEME - III

acid which yielded *two novel compounds,* ***2-[3-{2-(3,4-dimethoxyphenyl)ethenyl}-5-{3,4-dimethoxyphenyl}-2-pyrazolin-1-yl]thiocarboxamide (12)*** and ***2-[3-{2-(4-chlorophenyl)ethenyl}-5-{(4-chlorophenyl)}-2-pyrazolin-1-yl]thiocarboxamide*** **(14)**. In the former, the thiosemicarbazone **(11)** formed as intermediate being minor could not be isolated while in the latter, the thiosemicarbazone, ***N'[1,5-bis(4-chlorophenyl)pent-1,4-dien-3-ylidene]thiosemicarbazide*** **(13)** was isolated in poor yield **(SCHEME-III)**.

The structures of these compounds were established by IR, DCI-MS, ^{1}H-NMR and ^{13}C-NMR spectral studies.

CHAPTER - 3

2-[3,5-Disubstituted-2-Pyrazolinyl]thiazolin-4-ones from Chalcones

The compounds containing thiazolinone moiety are associated with diverse biological activities and were found to be very potent against a number of diseases such as antiulcer, antiinflammatory, anti-AIDS and antitubercular acitivity. In recent past, reactions of thiosemicarbazones of various aldehydes and ketones with α-chloroacetic acid and its functional derivatives in the presence of sodium acetate have been investigated and found to give the corresponding hydrazono-thiazolin-4-ones. However, the analogous reactions of 3,5-disubstituted-2-pyrazolinyl-thiocarboxamides with chloroacetic acid have not been described. Keeping in view of the importance of pharmaceutical applications and as part of our programme in search of biologically active compounds with sulphur and nitrogen containing heterocycles we have undertaken this problem.

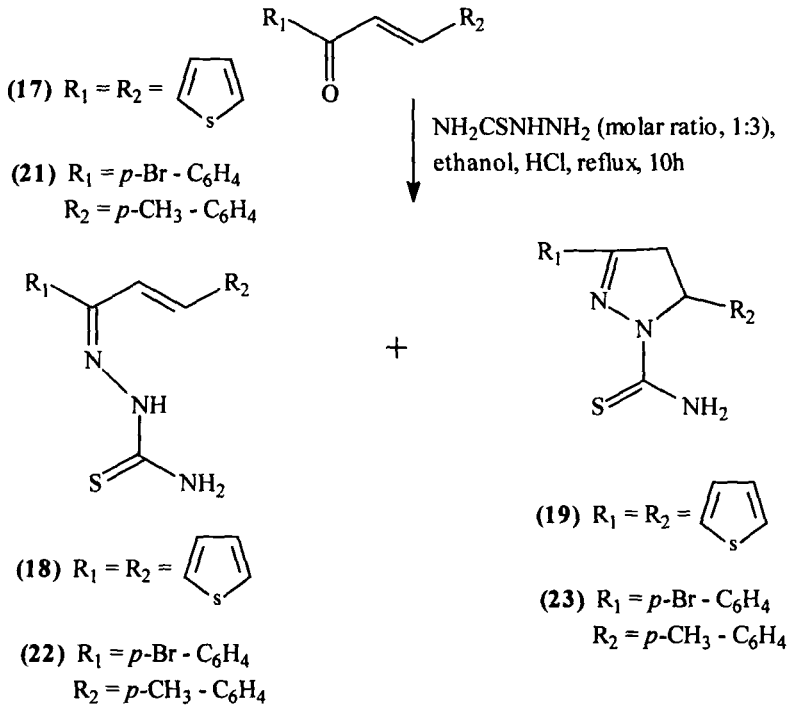
In continuation of our previous work described in CHAPTER-2 on the reactions of thiosemicarbazide with different *α,β*-unsaturated dienones to form novel compounds, 3,5-disubstituted-2-pyrazolin-1-yl-thiocarboxamides, we have extended the above reactions employing the 2-thienylchalcone and 4,4'-bromomethyl chalcone in place of dienones and condensing the thiocarboxamides moeity of 2-pyrazolinyl thiocarboxamides with chloroacetic acid in the presence of sodium acetate which yielded *two novel compounds,* ***2-[3,5-bis(2-thienyl)-2-pyrazolin-1-yl]thiazolin-4-one (20)*** and ***2-(3-(4-bromophenyl)-5-(4-methylphenyl)-2-pyrazolin-1-yl]thiazolin-4-one (24).***

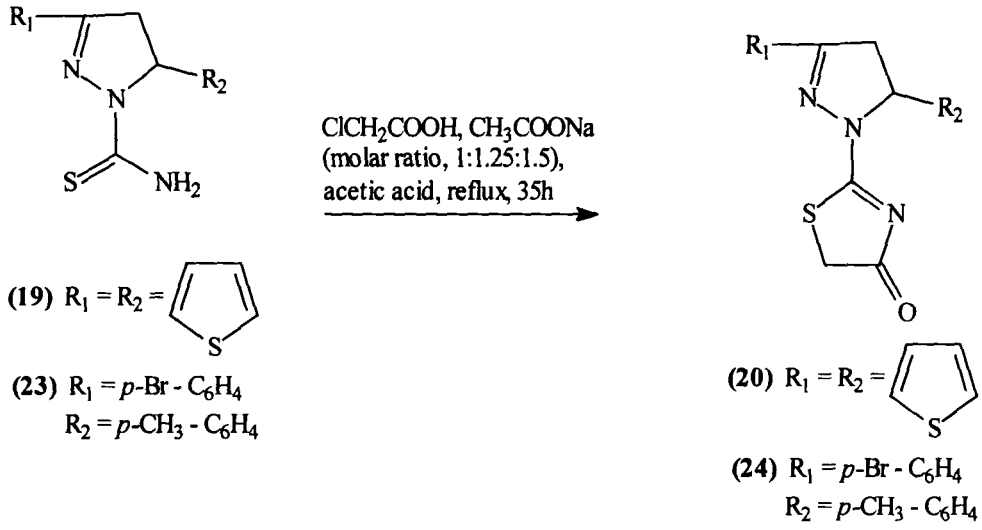
The reactions of these chalcones possessing α,β-unsaturated function were carried out in two steps.

Step 1 : The chalcone **(17)** and **(21)** were first reacted with thiosemicarbazide in the presence of conc. hydrochloric acid to yield N^1-[1,3-bis(2-thienyl) -2-propen-1-ylidene]thiosemicarbazide **(18)** and 2-[3,5-bis(2-thienyl) -2-pyrazolin-1-yl]thiocarboxamide in the former while N^1-[1-(4-bromophenyl)-3-(4-methylphenyl)-2-propen-1-ylidene]thiosemicarbazide **(22)** and 2-[3-(4-bromophenyl)-5-(4-methylphenyl)-2-pyrazolin-1-yl]thiocarboxamide **(23)** in the latter **(SCHEME-V)**.

Step 2 : The pyrazolinyl thiocarboxamides **(19)** and **(23)** were then treated with chloroacetic acid in the presence of sodium acetate to yield two novel compounds, 2-[3,5-bis(2-thienyl)-2-pyrazolin-1-yl]thiazolin-4-one **(20)** and 2-(3-(4-bromophenyl)-5-(4-methylphenyl)-2-pyrazolin-1-yl]thiazolin-4-one **(24)** respectively.

The structures of these products were established on the basis of spectral studies of FT-IR, DCI-MS, EI-MS, FAB-MS, ^{1}H-NMR and ^{13}C-NMR, spectral studies.


(17) R1 = R2 =
(21) R1 = p-Br - C6H4
R2 = p-CH3 - C6H4
NH2CSNHNH2 (molar ratio, 1:3),
ethanol, HCl, reflux, 10h
(18) R1 = R2 =
(22) R1 = p-Br - C6H4
R2 = p-CH3 - C6H4
(19) R1 = R2 =
(23) R1 = p-Br - C6H4
R2 = p-CH3 - C6H4

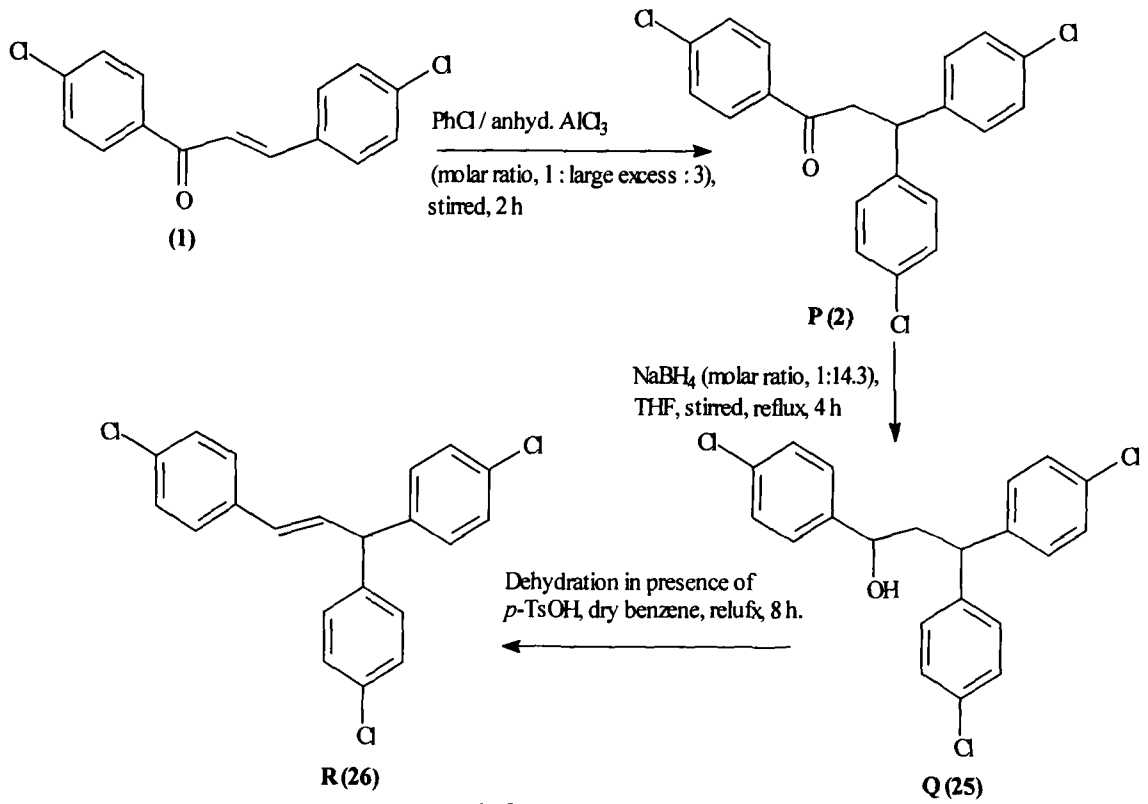

(19) R1 = R2 =
(23) R1 = p-Br - C6H4
R2 = p-CH3 - C6H4
ClCH2COOH, CH3COONa
(molar ratio, 1:1.25:1.5),
acetic acid, reflux, 35h
(20) R1 = R2 =
(24) R1 = p-Br - C6H4
R2 = p-CH3 - C6H4

SCHEME - V

CHAPTER - 4

1,3,3-Tris(p-chlorophenyl)propene from Chalcone

The toxicity of hydrocarbons is in general increased when the following elements or radicals are introduced into molecule, Cl, Br, I, OH, SH, SO_2, NO_2 and NH_2. Some of organochlorine compounds are reported potent insecticidal, antitumor, antimalarial and acaricidal. Keeping in view of the importance of organochlorine compounds, effort has been made for search of some new or improved organochlorine compounds as derivatives of chalcones. We report here the synthesis of ***1,3,3-tris(4-chlorophenyl)propan-1-ol (25) and 1,3,3-tris(4-chlorophenyl)prop-1-ene*** **(26)** from 4,4'-dichlorochalcone **(1) (SCHEME-VII).** The reaction were carried out in three steps.



SCHEME - VII

Step 1 : The adduct **(2)** was prepared from chalcone **(1)** using chlorobenzene in presence of anhydrous aluminium chloride exactly as described in CHAPTER-1.

Step 2 : The carbonyl group of the 1,3,3-tris(4-chlorophenyl)propan-1-one **(2)** was reduced with sodium borohydride in THF provided 1,3,3-tris(4-chlorophenyl)propan-1-ol **(25)**.

Step 3 : The dehydration of 1,3,3-tris(4-chlorophenyl)propan-1-ol **(25)** was carried out by refluxing it in dry benzene in the presence of a catalytic amount of *p*-toluenesulphonic acid furnished 1,3,3-tris(4-chlorophenyl)prop-1-ene **(26)**.

The structures of these compounds were established by IR, DCI-MS, FAB-MS, ^{1}H-NMR, ^{13}C-NMR spectral studies.

CHAPTER - 5

A Flavone from 1,3-Diketone (Baker-Venkataraman Transformation of 2-Benzolyloxyacetophenone) as an Undesired product in the Synthesis of Dithiazolidin-4-one

Flavonoids are widely distributed plant secondary metabolites and the field of flavonoids is one of the most fascinating area of plant chemistry. Their occurrence in nature, the chemical and biological relationship between them and the chemistry of their derivatives have been the subject of intensive study in recent past. These natural heterocyclic compounds possess a wide range of physiological and pharmacological properties, such as heart stimulant, antiviral, antihaemolytic activity, anthelmintic activity. In previous chapters we have synthesized 2-substituted-4-thiazolidinones as novel compounds from chalcones via their monoketo adduct using thioglycollic acid in the presence of ammonium carbonate in dry benzene.

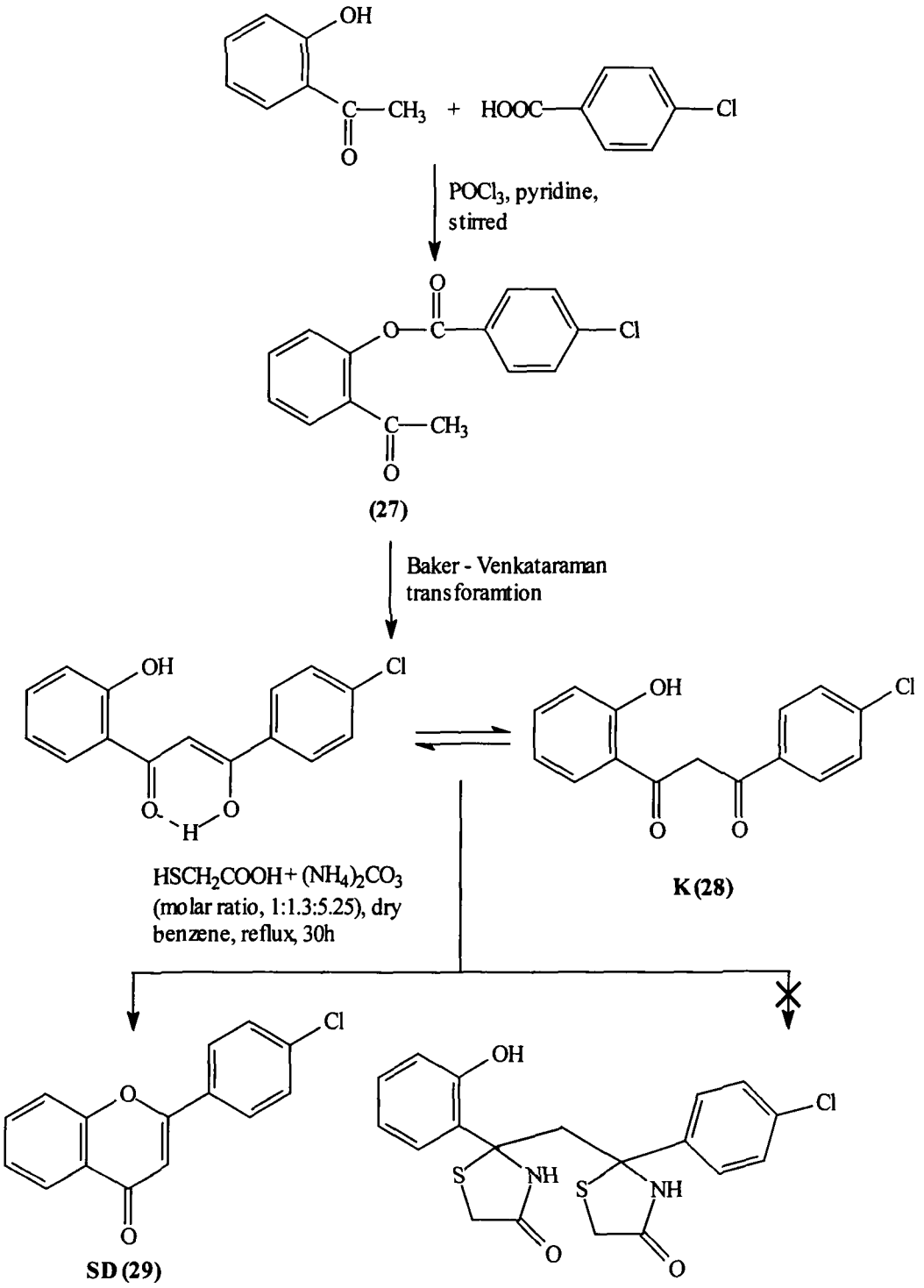
The aim of the present problem was to synthesize dithiazolidin-4-ones from 1,3-diketones using the same reagent. For this purpose, the precursor, 1,3-diketone **(28)** was reacted with thioglycollic acid and ammonium carbonate in dry benzene which afforded a ***4-chloroflavone*** **(29)** instead of the target compound, dithiazolidin-4-one. The ring closure of 1,3-diketone in acid medium to form flavone molecule is a well known reaction. From ^{1}H-NMR spectrum, it is found that the 1,3-diketone exists in the equilibrium mixture of keto-enol tautomeric forms **(SCHEME-VIII)**.

The reaction was carried out in two steps.

(i) The 1,3-diketone, 2-hydroxy-4'-chlorodibenzoyl methane **(28)** was first prepared by Baker-Venkataraman transformation of 2-(4'-chlorobenzoyloxy) acetophenone condensing *o*-hydroxyacetophenone with *p*-chlorobenzoic acid in the presence of a catalytic amount of $POCl_3$.

(ii) The 2-hydroxy-4'-chlorodibenzoyl methane **(28)** was then condensed with thioglycollic acid and ammonium carbonate in dry benzene afforded an undesired product, 4'-chloroflavone **(29)**. The target compound dithiazolidin-4-one could not be obtained in the reaction. The 1,3-diketone did not react with thioglycollic acid and ammonium carbonate, it simply cyclized to give a flavone which is a well known cyclization reaction in acetic medium **(SCHEME-VIII)**.

The structures of these compounds were established by DCI-MS, ^{1}H-NMR and ^{13}C-NMR spectral studies.


OH
C—CH3
O
+ HOOC
Cl
POCl3, pyridine,
stirred
O
O—C
Cl
C—CH3
O
(27)
Baker - Venkataraman
transforamtion
OH
Cl
O
O
H
HSCH2COOH+ (NH4)2CO3
(molar ratio, 1:1.3:5.25), dry
benzene, reflux, 30h
OH
Cl
O
O
K (28)
Cl
O
O
SD (29)
OH
Cl
S
NH
S
NH
O
O

SCHEME - VIII

CHATPER - 6

Biological Screening : Study for Anticancer and Antibacterial Activities

A. ANTICANCER ACTIVITY

The compounds **(2), (3), (9), (10), (12), (14), (19), (20)** and **(25)** have been evaluated for anticancer activity first in the 3-cell lines of three types of human cancers : breast (MCF7), Lung (NCI-H460) and CNS (SF-268) at one concentration as the one dose primary anticancer assay. The two compounds **(3)** and **(25)** out of these nine compounds tested have been found to be active in 3-cell line screening against breast (MCF7), Lung (NCI-M460) and CNS (SF-268) (Table-23). These two compounds were then tested against 60-cell lines of nine types of human cancers : leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast at five different concentrations. The compounds showed anticancer activity only at the higher conentration, 1 x 10^{-4}M. However, the compounds **(3)** has shown some activity in renal cancer even at lower concentration, 1 x 10^{-5}M. The compound **(2)** has shown significant anticancer activity in melanoma, colon and renal cancers, where the maximum reduction in growth is observed as 52, 80 and 91% respectively. The compound **(25)** has shown anticancer activity in melanoma and colon cancers, where the maximum reduction in growth is 48 and 83% respectively.

(B) ANTIBACTERIAL ACTIVITY

A total of five compounds were tested against three Gram +ve bacteria (*Streptococcus viridans*, *Staphylococcus epidermatis* and *Bacillus subtilis* and one Gram -ve bacteria (*Escherichia coli*). The varying level of

antibactrial activity was detected against one or more test organisms. Solvent control (DMSO) showed non-significant inhibition to test microorganisms.

All the five compounds demonstrated activity against both Gram +ve and Gram -ve bacteria. The compounds exhibited antibacterial activity in the concentration range 200 μg to 400 μg/100 μl. Overall broad spectrum antibacterial activity i.e. active against Gram +ve and Gram -ve was deduced in five compounds. These compounds may be directly explored in the preparation of topical antiinfective agents. However, further exploration requires detailed study on exact MIC values and least toxicity to host cell and system.

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FACULTY OF SCIENCE
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ALIGARH (INDIA)

2003

DEDICATED

TO

MY PARENTS

DEPARTMENT OF CHEMISTRY
ALIGARH MUSLIM UNIVERSITY
ALIGARH—202 002
(U. P.) INDIA

Phones {Ext. (0571) 7 0 3 5 1 5
{Int. 317, 318

Dated 23-6-2003

Certificate

I certify that the work presented in this thesis entitled ***"Design and Synthesis of Biologically Active Compounds with Sulphur and Nitrogen Containing Heterocycles and Related Compounds"*** has been carried out by **Mr. Shishupal Singh** under my supervision. It is original in nature and has not been submitted for any other degree.

(Prof. W.H. Ansari)

Acknowledgements

I bow my head with all humility and reverence to the Almighty for the completion of this task.

Words fail to express my indebtedness that I owe to my erudite research guide, Prof. Wajid Husain Ansari, who inspired to take up this task. I will cherish throughout my life the valuable suggestions, constructive criticism and unending support that I received from him throughout the course of this study.

I wish to place on record the kind help received from Prof. Shafiullah and Prof. M. Ilyas, who as Chairmen of the Department provided all the necessary facilities for undertaking this research problem.

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Dr. Rakesh Kumar, Dr. Yogesh Kumar, Dr. Ritu Singh, Dr. Qamaruddin, Dr. Manish Agrawal. The beautiful and nice moment spent with Hemraj Singh, Rajkumar Singh, Surjan Singh, Vijay Singh, Phool Prakash Singh will be cherished throughout my life. Heartful thanks are due to Mr. Dinesh Kumar, Km. Survesh, Km. Nirvesh, Km. Veervati, Km. Meena, Km. Rekha, Mrs. Seema Verma for their pleasant companionship. I owe a lot to Miss Monika and Km. Pooja for being a constant source of inspiration and moral support.

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(Shishupal Singh)

C O N T E N T S

[Synthesis, Structure Elucidation and Biological Screening]

GENERAL INTRODUCTION

Heterocyclic compounds are very widely distributed in nature and are essential to life as they play a vital role in the metabolism of all living cells. Thus, for example, the following are heterocyclic compounds : the pyrimidine and purine bases of the genetic material DNA; the essential amino acids proline, histidine and tryptophan; the vitamins and coenzyme precursors thiamine, riboflavine, pyridoxine, folic acid and biotin; the B_{12} and E families of vitamin; the photosynthesizing pigment chlorophyll; the oxygen transporting pigment haemoglobin, and its breakdown products, the bile pigments; the hormones kinetin, heteroauxin, serotonin and histamine, together with most of the sugars. There are a vast number of pharmacologically active heterocyclic compounds, many of which are in regular clinical use. Some of these are natural products, for example antibiotics such as penicillin and cephalosporin, alkaloids such as vinblastine, ellipticine, morphine and reserpine and cardiac glycosides such as those of digitalis. However, the large majority are synthetic heterocyclics which have found widespread use, for example as anticancer agents, analeptics, analgesics, hypnotics and vasopressor modifiers, and as pesticides, insecticides, weedkillers and rodenticides.

There is also a large number of synthetic heterocyclic compounds with other important practical applications, as dyestuffs, copolymers, solvents, photographic sensitizers and developers, as antioxidant and vulcanization accelerators in the rubber industry and many are valuable intermediates in synthesis.

The broad spectrum of biological activities associated with these compounds and the multiplicity of action displayed by certain individual

members make them one of most interesting class of compounds. The current research in organic chemistry and closely allied branches of biology is characterized by extensive investigation of physiologically active compounds encountered in the plant and animal world. The search for these active constituents which control the biological process of various systems have acted as a powerful stimulus to the further development of the chemistry of heterocyclic compounds. Synthesizing any useful organic compound is easier than to isolate the same from natural resources. Therefore, in recent years much effort are being applied by chemists in synthesizing such organic compounds which possess high degree of biological activities. Innumerable heterocyclic compounds have been prepared across the world for better therapeutics, particularly the compounds having hetero atoms such as O, S and N.

A study on the influence of structure on activity shows that sometimes a minor change in heterocyclic nuclei enhances the pharmacological profile many folds than the parent nuclei. The search for new efficient and safe nuclei leads to an improvement in the existing drugs by increasing their potency, duration of action and decreasing side effects as well as creating new biologically active agents by molecular modification.

The successful application of heterocyclic compounds in these and many other ways and their appeal as materials in applied chemistry and in more and fundamental and theoretical studies ensures virtually limitless series of structurally novel heterocyclic compounds with wide range of physical, chemical and biological properties.

Keeping in view of the importance of heterocyclic compounds, we have undertaken this problem on "Design and Synthesis of Biologically Active Compounds with Sulphur and Nitrogen Containing Heterocyles".

Chapter - 1

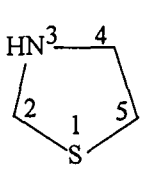
2,2-Disubstituted Thiazolidin-4-ones from α,β-Unsaturated Enones

Theoretical

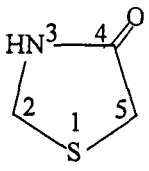
THEORETICAL

Heterocyclic compounds are those which have a cyclic structure with two, or more, different kinds of atoms in the ring. Since the ring can be of any size, from three-membered upwards, and since the heteroatoms can be drawn in almost any combination from a large number of the elements (though nitrogen, oxygen and sulfur are the most common), the number of possible heterocyclic systems is almost limitless. The search for physiologically active compounds which control the biochemical process of different systems have acted as a powerful stimulant for the development of the chemistry of heterocyclic compounds. Compounds with sulphur and nitrogen containing heterocycles form an important and fascinating group of heterocyclic compounds of diverse biological activities.

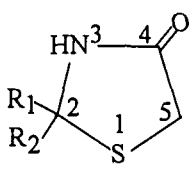
4-Thiazolidinones belong to an important class of biologically active five membered sulphur and nitrogen containing heterocyclic compounds with a carbonyl group in the 4-position(**II**). These are the derivatives of thiazolidine(**I**).



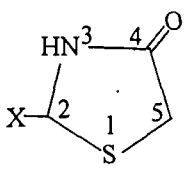
I



II



III



IV

R_1/R_2=alkyl/aryl

IVA, X = O (2,4-thiazolidin-dione)
IVB, X = S (2-thiono-4-thiazolidinone or rhodanine)
IVC, X = NR (2-imino-4-thiazolidinone or pseudothiohydantoin)

IVD, X = N-N=C$\begin{matrix} R \\ R_1 \end{matrix}$ (hydrazino as 4-oxo-2-thiazolin-2-ylhydrazone of the carbonyl compound).

Substituents in the 2, 3 and 5-positions may be varied, but the greatest difference in structures and properties is exerted by the group attached to the carbon atom in the 2-position (R_1 and R_2 in formula **III** and X in formula **IV**). Variations in the substituents attached to the nitrogen atom and the methylene carbon atom are possible for the structures represented by formulas **III** and **IV**.

4-Thiazolidinones have been the subject of extensive study in the recent past. Numerous reports in the form of chemical reviews[1,2] and review articles[3,4] have appeared in the literature which highlight their chemistry and use, especially syntheses, reactions and biological activity. 4-Thiazolidinone derivatives have been found to be associated with diverse biological activities such as bactericidal[5-10], fungicidal[7-9,11], insecticidal[12-14], pesticidal[15], herbicidal[16-18], amoebicidal[19] antitubercular[20-21], antiinflammatory[22-26], antitumor[27-28], antipsychotic[29-31], antiviral[32-34], anti-convulsant[19,35-38], anthelmintic[39-40] respiratory activity[29,41] antidiarrhoeal[42] and antiarthritic[43]. A number of thiazolidinone derivatives has also been found to exhibit highly potent anti-PAF[44-45], anti-histaminic[46-48], antidiabetic[49-50], oxygenase inhibitory[51], calcium antagonist[52], potassium inhibitory[53] PPAR agonist[54], cardioprotective[55], antiischemic activity[56-57] and a promising agent for treating Alzheimer disease[50], cancer[58] and viral diseases like AIDS[33-34,58] and hepatitis-B[33].

Several methods for the preparation of 4-thiazolidinones have been reported in the literature[1,2] which are based mainly on the reaction of:-

1. α-mercaptoalkanoic acids with

(a) Schiff bases

(b) isothiocynates

(c) isocynates

(d) cyanamide

2. α-halo- or α-hydroxyalkanoic acids, α, β-unsaturated acids or their derivatives with

(a) dithiocarbamates

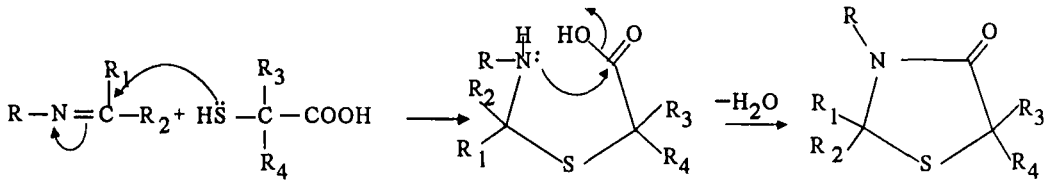
(b) thiocarbamates

(c) thioureas

(d) thiosemicarbazones

(e) alkali thiocynates

α-Mercaptoalkanoic acids have been extensively used for the synthesis of 4-thiazolidinones. The substituted and unsubstituted α-mercapto alkanoic acids react conveniently with Schiff bases of aromatic or heterocyclic aldehydes or ketones and aliphatic or aromatic amines in different solvents to give a variety of 2-substituted-4-thiazolidinones(**V**)[8,10,45,46,59-66].

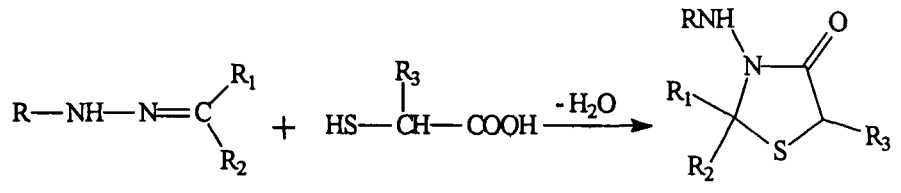


V

R = alkyl, aryl or heterocyclic group
R_2 = H, alkyl or aryl

R_1 = alkyl, aryl or heterocyclic
R_3 = H, alkyl, aryl
R_4 = H, alkyl

Hydrazones of aldehydes or ketones react with substituted or unsubstituted α-mercapto alkanoic acids to form 2-substituted or 2,2-disubstituted 4-thiazolidinones(**VI**)[5,67-73].

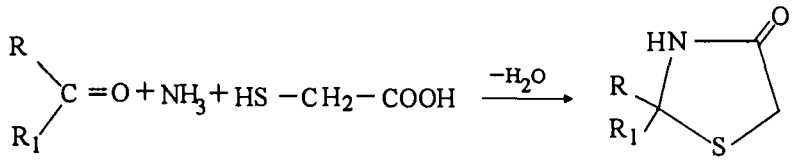


VI

R = alkyl, aryl or heterocyclic
R_2 = alkyl, aryl or heterocyclic

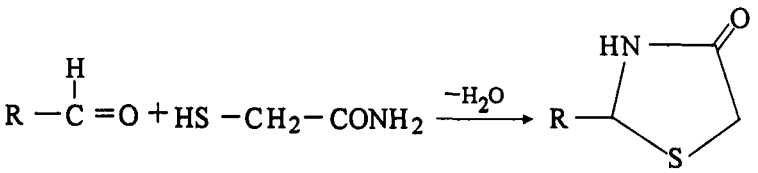
R_1 = H, alkyl, aryl or heterocyclic
R_3 = H, alkyl

α-Mercaptoacetic acid reacts with the aldehyde or ketone in the presence of ammonium salts such as ammonium carbonate or acetate in inert solvent. The reaction seems to proceed by the formation of an aldimine or a ketimine intermediate followed by the cyclisation with α–mercaptoacetic acid to form 2,2-disubstituted-4-thiazolidinones(**VII**)[63,74-76].



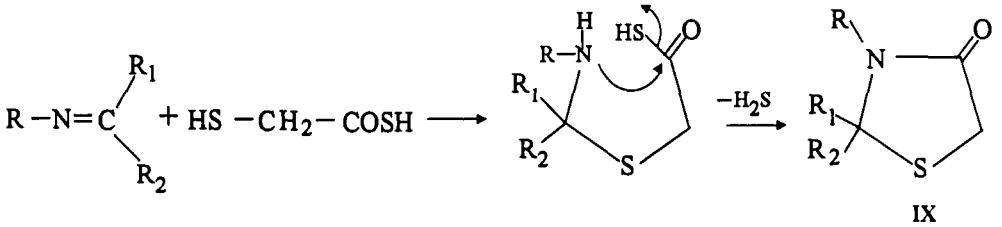
R=H or alkyl R_1=alkyl or aryl VII

α-Mercaptoacetamide reacts with the carbonyl function of aldehydes in the presence of catalytic amounts of *p*-toluenesulphonic acid or boron trifluoride ethereate in inert solvent to give 2-substituted-4-thiazolidinones(**VIII**)[20,78,79].



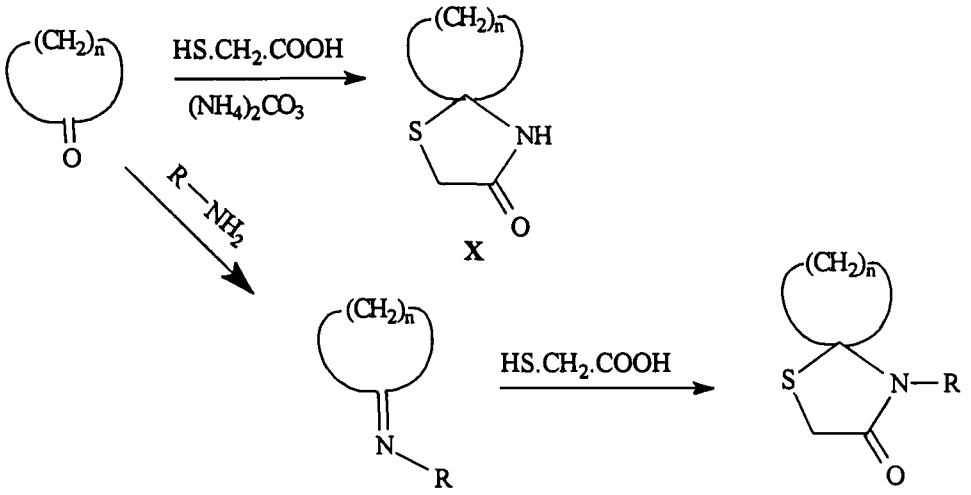
R=alkyl or aryl VIII

α-Mercaptothiocarboxylic acids can also be used for the synthesis of 4-thiazolidinones(**IX**) by the reaction with different Schiff bases[80].



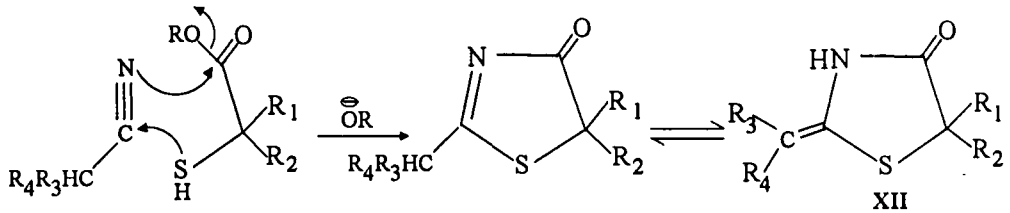
R=alkyl or aryl R_1=H or alkyl R_2=alkyl or aryl

A number of spiro-4-thiazolidinones(**X, XI**) has been prepared by the reaction of cyclic ketones with α-mercaptoacetic acid in the presence of ammonium carbonate or substituted amines[78,80-81].



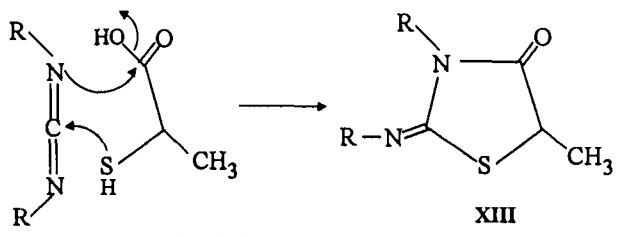
R = Alkyl or aryl

Substituted and unsubstituted α-mercaptoacetic acid, esters react smoothly with the compounds containing activated nitrile groups in the presence of an equivalent amount of alcoholate to give 4-thiazolidinones(**XII**)[85].



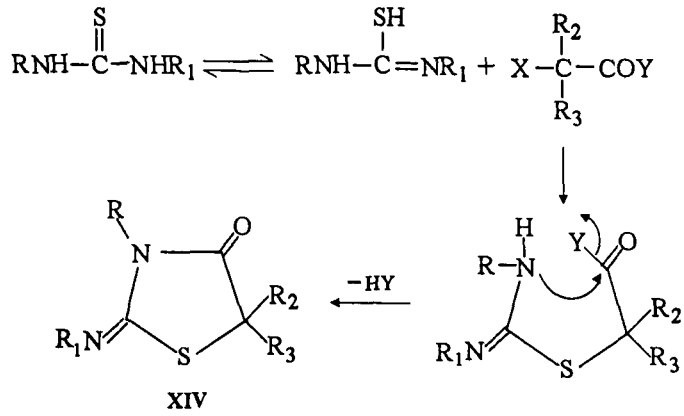
R=CH_3 or C_2H_5 R_1=H or C_2H_5 R_2 = H, C_2H_5, Ph or O-$CH_3C_6H_4$
R_3=H or Ph R_4= - COOEt, - $CONH_2$, - CN, Pyridyl, Indoyl or Ph

Monforte et al.[86] have synthesized 4-thiazolidinones by reacting carbodiimides with α-mercaptopropanoic acid. The acid reacts with one of the two carbodiimidic C=N groups to give 3-substituted-2-imino-5-methyl-4-thiazolidinones(**XIII**).



R=alkyl or aryl

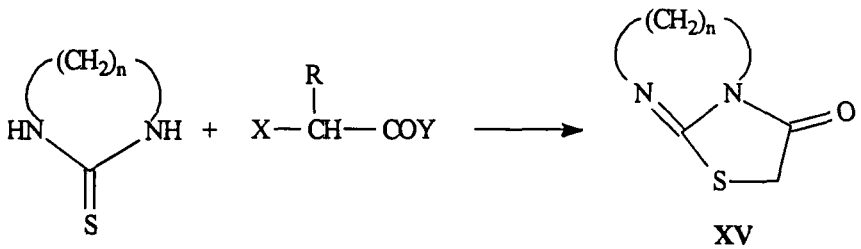
Substituted 2-imino-4-thiazolidinones(**XIV**) are obtained in good yields by the reaction of symmetrical and unsymmetrical thioureas with various substituted and unsubstituted α-haloalkanoic acids, their esters, acid chlorides, amides and carbamates. The reaction proceeds via the intermediate isothiourea which cyclise in the presence of sodium acetate or pyridine[87-93].



XIV

R=alkyl, aryl or heterocyclic R1=alkyl, aryl or heterocyclic
R_2=H or alkyl R_3=H or alkyl

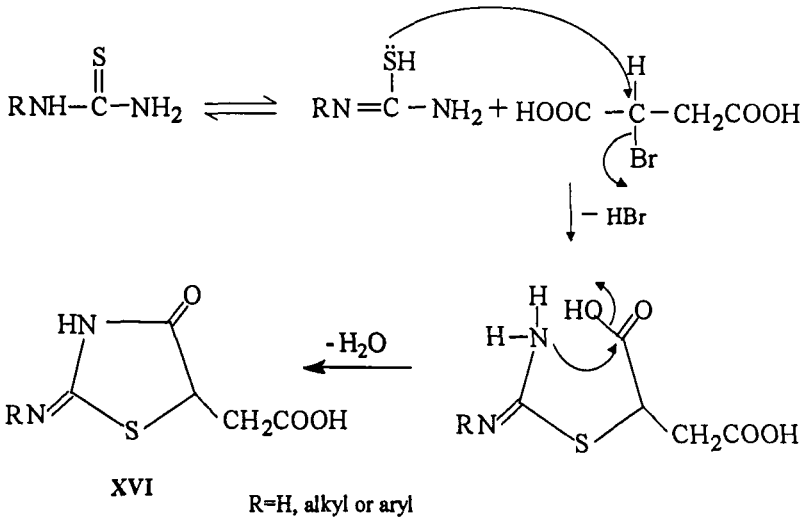
A number of fused thiazolidin-4-ones(**XV**) has been prepared by the reaction of cyclic thioureas with various substituted α-haloalkalnoic acids and their derivatives[94-100].



XV

R = H or alkyl
X = Halo-
Y = Cl or OR

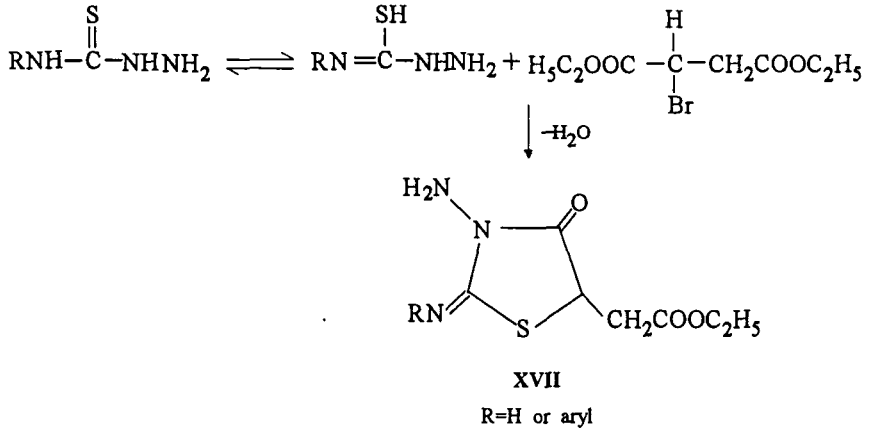
2-Imino-4-oxo-5-thiazolidinone acetic acid(**XVI**) can be conveniently prepared from dicarboxylic acids[101]. α-Bromosuccinic acid on treatment with thioureas in the presence of sodium acetate in methanol gives 2-imino-4-oxo-5-thiazolidinone acetic acid.



XVI

R=H, alkyl or aryl

Recently, Madhukar S. Chande et al.[102] have synthesized 3-amino-2-alkyl/arylimino-5-carbethoxy methyl thiazolidin-4-one (**XXII**) by the reaction of diethyl bromomalonate (DBM) with 4-aryl substituted thiosemicarbazide in ethanol in the presence of pyridine.

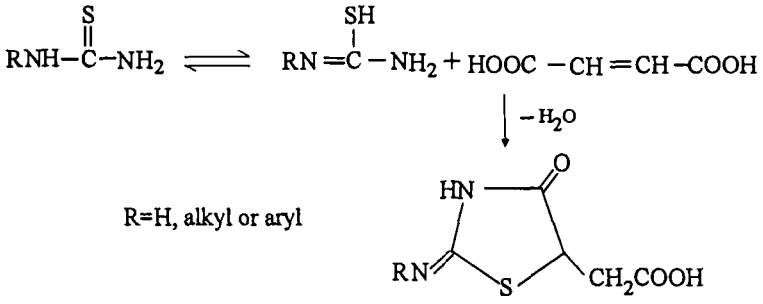


XVII

R=H or aryl

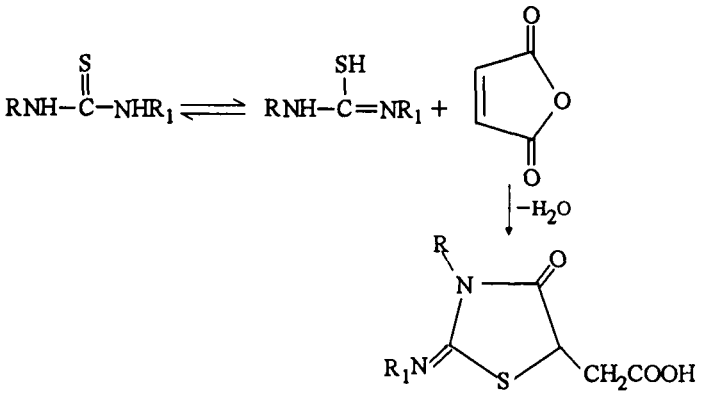
Thioureas add to the unsaturated carbon-carbon linkage of maleic, fumaric, citraconic acids, their esters and imides probably by a Michael type

reaction and cyclisation gives a 2-imino-4-oxo-5-thiazolidineacetic acid(**XVIII**)[103,104].



XVIII

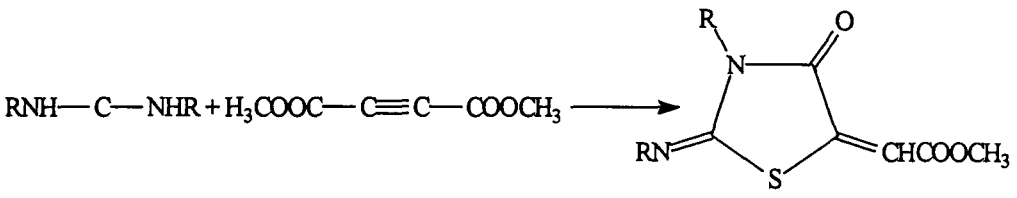
2-Imino-4-oxo-5-thiazolidineacetic acid (**XIX**) can also be synthesized in good yields by refluxing equimolar amounts of substituted and unsubstituted thioureas and maleic anhydride in acetone[105-106].



XIX

R=H, alkyl or aryl R_1=H, alkyl or aryl

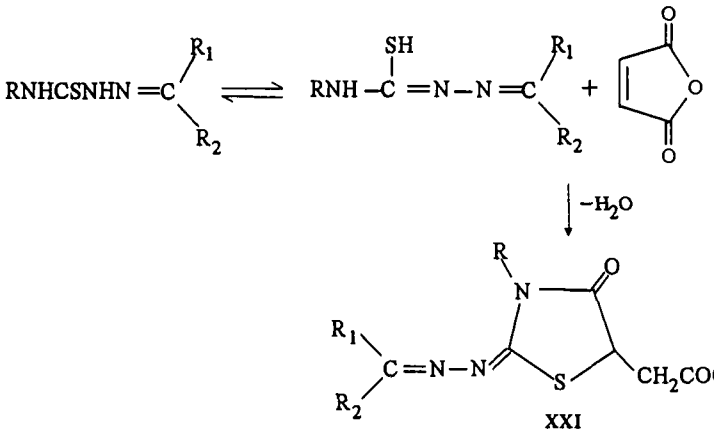
Dimethyl acetylenedicarboxylate (DMAD) reacts readily with substituted thioureas, thiosemicarbazides and thiosemicarbazones to give 4-thiazolidinones(**XX**)[107]



R = H, CH_3, $C_6H_5CH_2$ or C_6H_5

XX

As with thioureas, thiosemicarbazones of aldehydes or ketones react with maleic anhydride in refluxing benzene or toluene and form the 5-carboxy-methyl-4-oxo-2-thiazolin-2-ylhydrazone (**XXI**) of the carbonyl compounds[113].

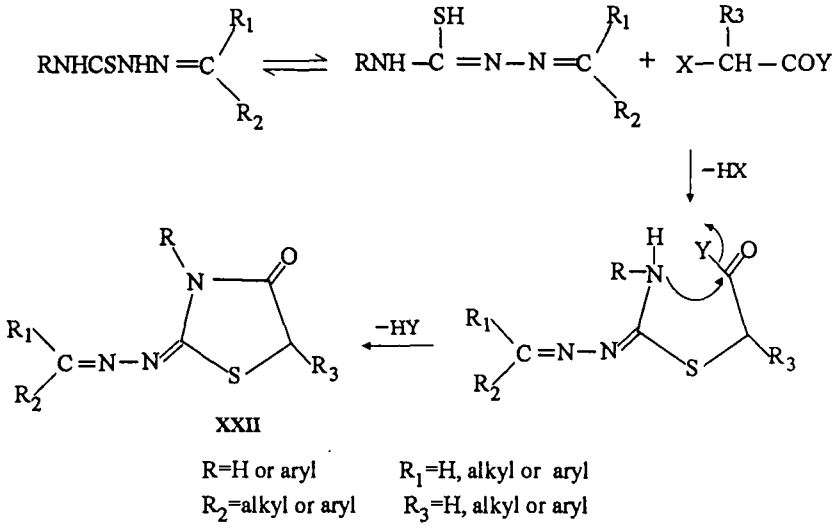


XXI

R=H or aryl R_1=H, alkyl, aryl or Heterocyclic

R_2=alkyl or aryl

When the thiosemicarbazone of aldehyde or ketone is allowed to react with substituted and unsubstituted α-haloalkanoic acids, their esters, amides in the presence of sodium ethoxide or sodium acetate, the product formed is aldehyde or ketone derivative of 2-hydrazino-4-thiazolidinones (**XXII**)[108,109].

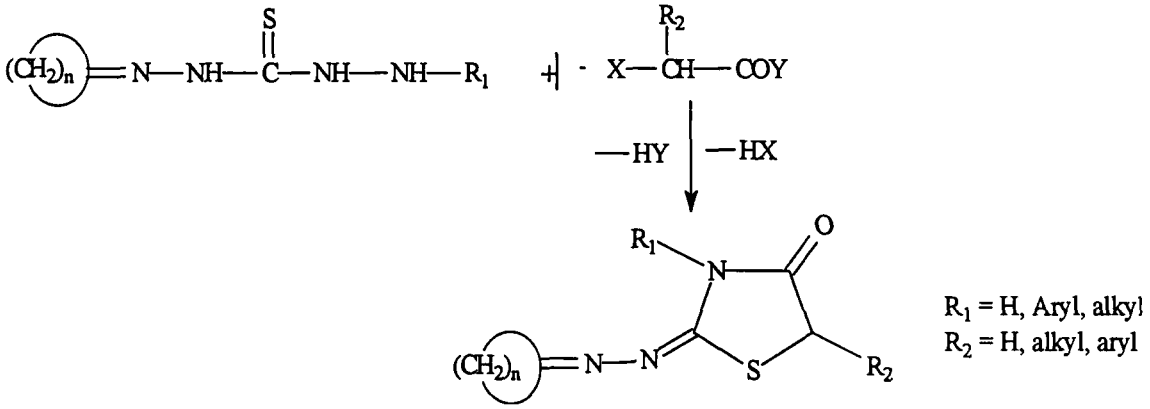


XXII

R=H or aryl R_1=H, alkyl or aryl

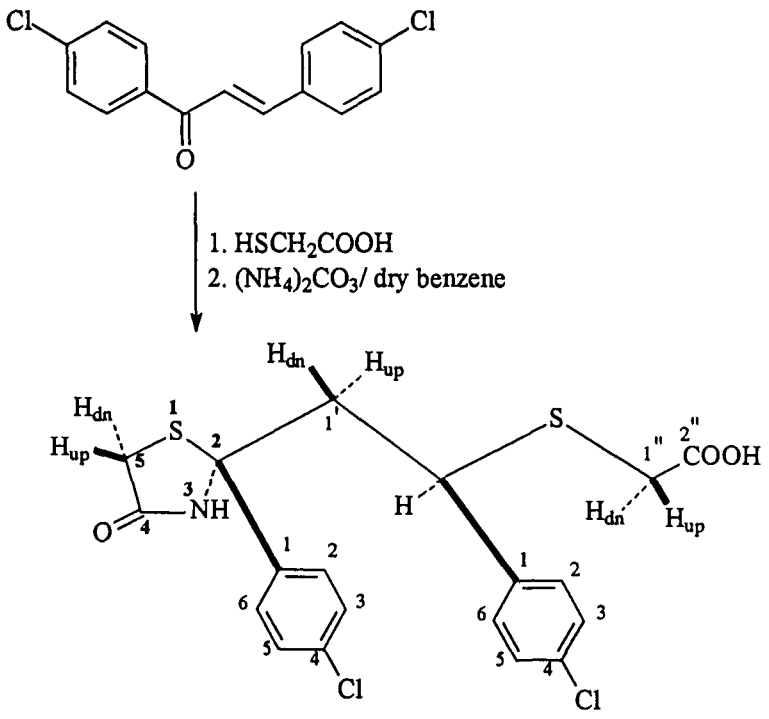
R_2=alkyl or aryl R_3=H, alkyl or aryl

A number of extranuclear thiazolidin-4-ones(**XXIII**) has been prepared by the reaction of thiosemicarbazones of cyclic ketones with substituted and unsubstituted α-haloalkanoic acids in the presence of sodium acetate or sodium ethoxide[110-112].



XXIII

Recently, W.H. Ansari and co-workers[114] have synthesized a novel compound 2-[2-carboxymethylthio-2-(4-chlorophenyl)ethyl]-2-(4-chlorophenyl)-4-thiazolidinone (**XXIV**) from p,p'-dichlorochalcone.



XXIV

Discussion

DISCUSSION

SUMMARY

The work included in this chapter deals with the synthesis of following four novel compounds –

i) 2-[2,2-Bis(4-chlorophenyl)ethyl]-2-(4-chlorophenyl) thiazolidin-4-one(3), from 4,4'-dichlorochalcone(1) via 1,3,3-tris(4-chlorophenyl) propan-1-one(2) using mercaptoacetic acid.

ii) 2,2-Di[2-(4-chlorophenyl)-2-(3,4-dimethoxyphenyl)ethyl]thiazolidin-4-one(6), from 1,5-bis(3,4-dimethoxyphenyl)pent-1,4-dien-3-one (4) via 1,5-bis(4-chlorophenyl)-1,5-bis(3,4-dimethoxyphenyl)pentan-3-one (5) using mercaptoacetic acid.

iii) 2,2-Di[2-(4-chlorophenyl)-2-(3,4-dimethoxyphenyl)ethyl]-5-(methyl) thiazolidin-4-one(7), from (4) via (5) using α-mercaptopropionic acid and

iv) 2,2-Di[2,2-bis(4-chlorophenyl)ethyl]-5-(methyl)thiazolidin-4-one(10) from 1,5-bis(4-chlorophenyl) pent-1,4-dien-3-one(8) via 1,1,5,5-tetra (4-chlorophenyl) pentan-3-one(9) using α-mercaptopropionic acid, all in the presence of ammonium carbonate as a source of ammonia.

Structures are established on the basis of IR, Mass, ^{1}H-NMR, ^{13}C-NMR and 2D-NMR (COSY, HETCOR, LONG RANGE HETCOR, APT) spectral studies. The compounds (2), (3), (9) and (10) have been evaluated for anticancer activity and compound (3) and (10) for antibacterial activity.

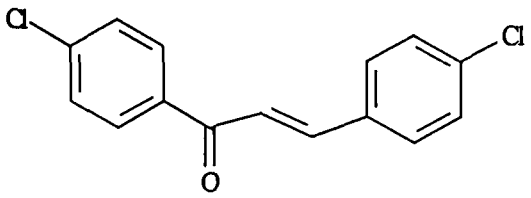
INTRODUCTION

In recent years, it has been found that the interest in thiazolidin-4-ones for medical applications is increasing strongly. Thiazolidin-4-ones substituted in the 2-position, viz (–)2-(5-carboxypentyl)-4-thiazolidinone (originally isolated[20] from the culture broth of a strain of *streptomyces* and used as a new antibiotic in the name of actithiazic acid), its derivatives and analogues[20] have exhibited unusually high *in vitro* acitvity against *Mycobacterium tuberculosis*. In their syntheses[20], α-mercaptoacetamide was used instead of

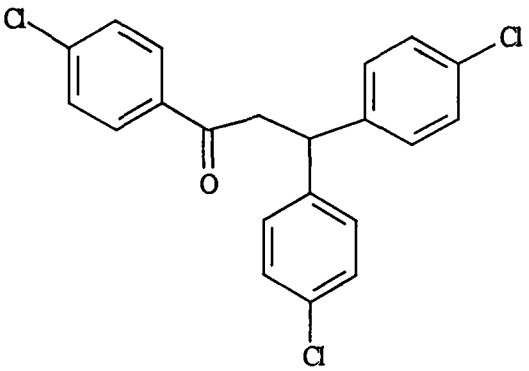
α-mercaptoacetic acid for the reaction with carbonyl compounds in the presence of a catalytic amount of *p*-toluenesulphonic acid in refluxing benzene or toluene with azeotropic removal of water. A number of 2-pyridyl substituted 4-thiazolidinones has been synthesized by Tanabe *et al.*[45] in 1995 following the method of Surrey[74], condensing α-mercaptoalkanoic acids with aldehydes and primary amines or with corresponding Schiff bases and found to exhibit highly potent and selective anti-Platelet Activating Factor activity[44,45] both *in vitro* and *in vivo*. During the past few years, some biologically potential thiazolidin-4-ones have been synthesized and found to possess anticonvulsant[19,35-38], antidiarrhoeal[42], antihistaminic[46-48], antimicrobial[5-10], oxygenase inhibitory[51] and calcium antagonist activity[52]. Because 4-thiazolidinones substituted in the 2-position were proven to be biologically very potent and selective and as part of our programme in search of biologically active compounds with nitrogen and sulphur containing heterocycles, we have undertaken this problem. It deals with the synthesis of *four novel compounds*, *2-[2,2-bis(4-chlorophenyl)ethyl]-2-(4-chlorophenyl) thiazolidin-4-one* **(3)**, *2,2-di[2-(4-chlorophenyl)-2-(3,4-dimethoxyphenyl)ethyl]thiazolidin-4-one* **(6)**, *2,2-di[2-(4-chlorophenyl)-2-(3,4-dimethoxyphenyl)ethyl]-5-(methyl)thiazolidin-4-one* **(7)** *and 2,2-di[2,2-bis(4-chlorophenyl)ethyl]-5-(methyl)thiazolidin-4-one* **(10)**. The compound **(3)** has been obtained from *4,4'-dichlorochalcone* **(1)** via *1,3,3-tris(4-chlorophenyl)propan-1-one* **(2)** using mercaptoacetic acid. Compounds **(6)** and **(7)** both from *1,5-bis(3,4-dimethoxyphenyl)pent-1,4-dien-3-one* **(4)** via *1,5-bis(4-chlorophenyl)-1,5-bis(3,4-dimethoxyphenyl)pentan-3-one* **(5)** using mercaptoacetic acid in the former and α-mercaptopropionic acid in the latter and the compound **(10)** from *1,5-bis(4-chlorophenyl)pent-1,4-dien-3-one* **(8)** via *1,1,5,5-tetra(4-chlorophenyl)pentan-3-one* **(9)** using

α-mercaptopropionic acid, all in the presence of ammonium carbonate as a source of ammonia.

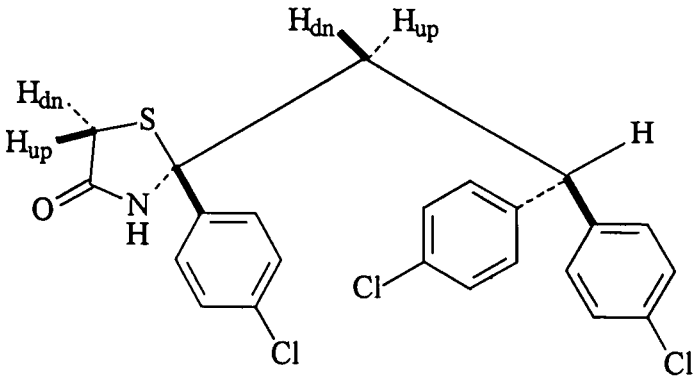
Structural assignments, stereochemistry and biological assay are discussed. Screening results of compounds **(2)**, **(3)**, **(9)** and **(10)** are summarized for anticancer activity against 3-cell lines of three types of human cancers : lung, breast and CNS and the results of **(3)** are also summarized for anticancer activity against 60-cell lines of nine types of human cancers : leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast. Screening results of **(3)** and **(10)** are also summarized for antibacterial activity against four bacteria *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus epidermatis* and *Streptococcus viridans* **(DETAILS IN CHAPTER-6)**.



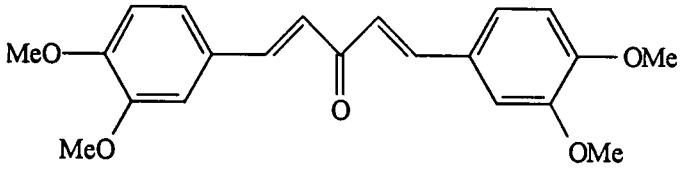
(1)



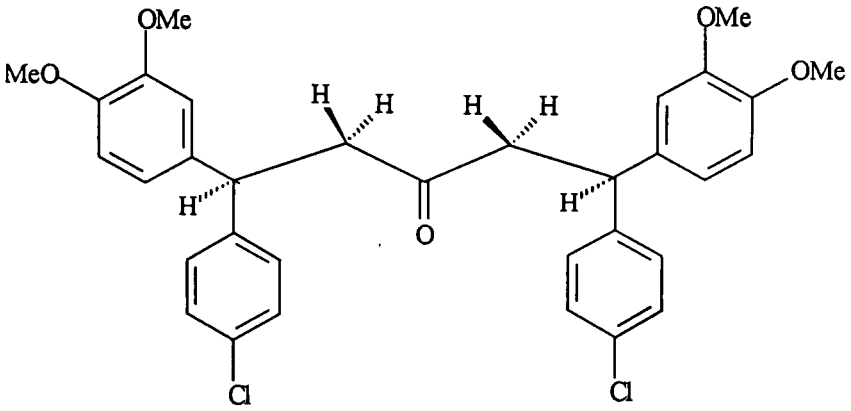
(2)


Hdn
Hup
Hdn
Hup
S
O
N
H
Cl
H
Cl
Cl

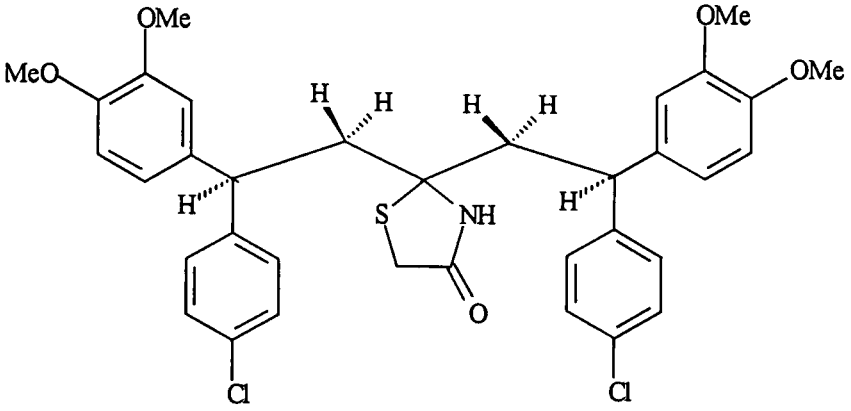
(3)


MeO
MeO
O
OMe
OMe

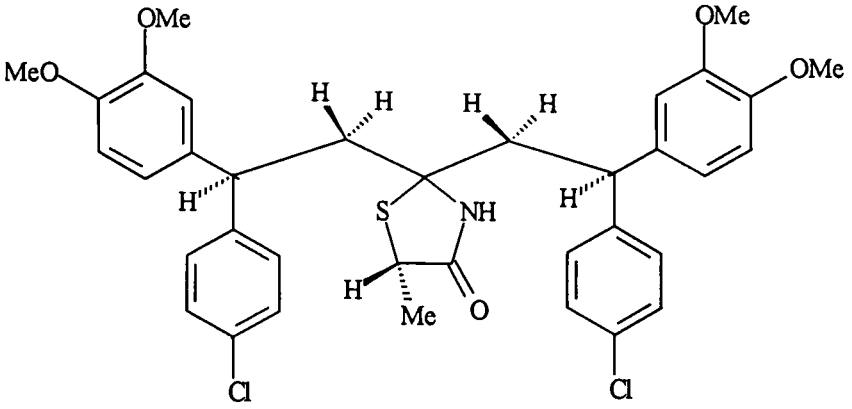
(4)


OMe
MeO
H
H
H
H
H'
H'
O
OMe
OMe
Cl
Cl

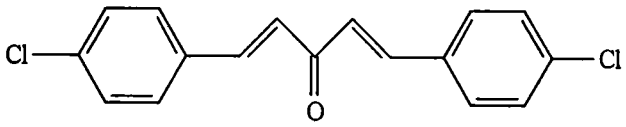
(5)


OMe
MeO
H
H
H
H
H'
H'
S
NH
O
OMe
OMe
Cl
Cl

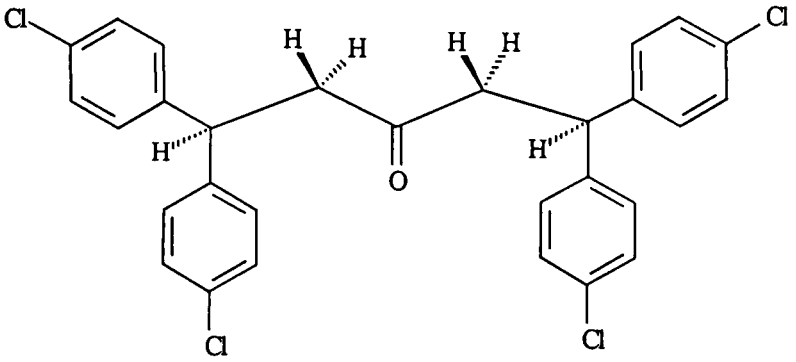
(6)


OMe
MeO
OMe
OMe
H
H
H
H
H
H
S
NH
H
Me
O
Cl
Cl

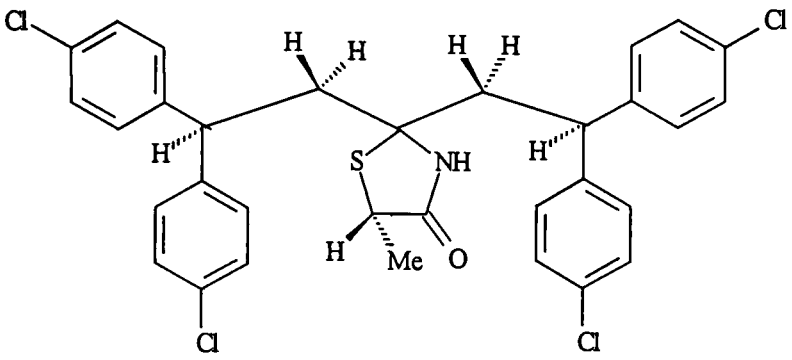
(7)


Cl
O
Cl

(8)


Cl
H
H
H
H
H
H
O
Cl
Cl

(9)


Cl
H
H
H
H
H
H
S
NH
H
Me
O
Cl
Cl

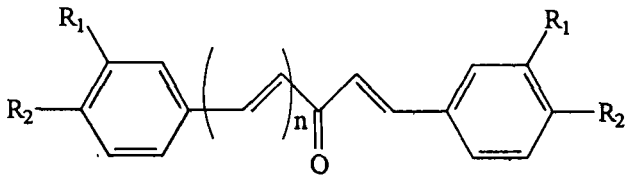
(10)

RESULTS AND DISCUSSION

The syntheses of target compounds **(3)**, **(6)**, **(7)** and **(10)** were performed in two steps **(SCHEME-I)**.

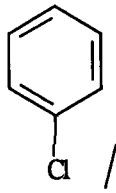
Step 1 : The adducts **(2)**, **(5)** and **(9)** were first prepared following a literature procedure[122] by the reaction of the corresponding enones **(1)**, **(4)** and **(8)** with dry chlorobenzene in the presence of anhydrous aluminium chloride (molar ratio, 1:large excess[122]:3) at room temperature, in good yields (~66%, 70%, 76%).

Step 2 : The adducts **(2)**, **(5)** and **(9)** were then condensed with α-mercaptoalkanoic acids and ammonium carbonate (molar ratio, 1:1.30:5.25) by refluxing in dry benzene for 40-45 h with azeotropic removal of water and the products purified by column chromatography over silica gel using pet. ether-diethylether as eluent and then crystallized to yield the desired products (~58% yields). The compounds **(6)** and **(7)** both were obtained from the same adduct **(5)** by condensing with mercaptoacetic acid and α-mercaptopropionic acid while **(3)** and **(10)** from the adducts **(2)** and **(9)** by condensing with mercaptoacetic acid and α-mercaptopropionic acid respectively.

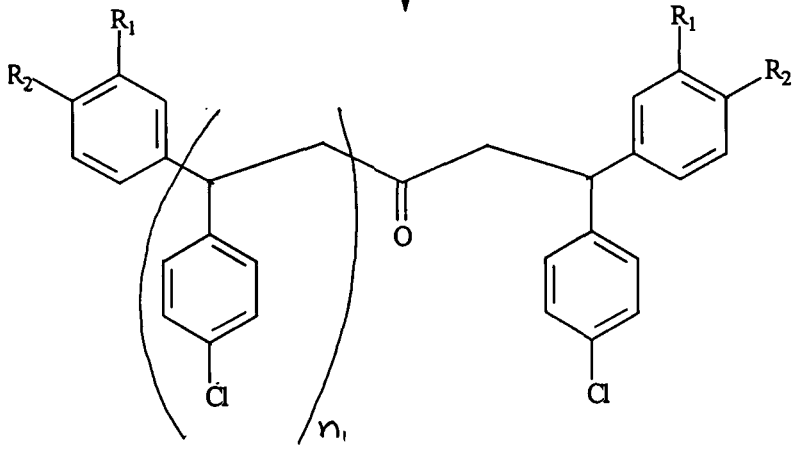


1) $R_1 = H, R_2 = Cl, n = 0$
4) $R_1 = R_2 = OMe, n = 1$
8) $R_1 = H, R_2 = Cl, n = 1$

Step 1



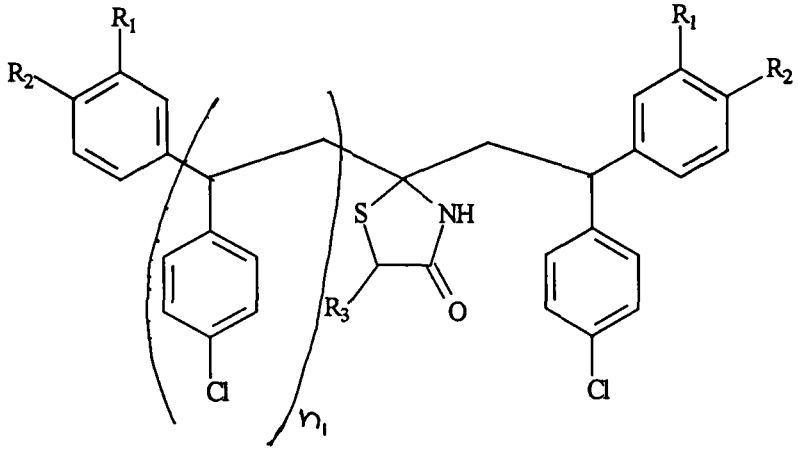
anhyd.$AlCl_3$ (molar ratio, 1: large excess[122] : 3), stirred at r.t., 3-8 h.



2) $R_1 = H, R_2 = Cl, n_1 = 0$
5) $R_1 = R_2 = OMe, n_1 = 1$
9) $R_1 = H, R_2 = Cl, n_1 = 1$

Step 2

dry benzene, reflux, 40-45h.
(R_3 = H, mercaptoacetic acid or thioglycollic acid
$R_3 = CH_3$, α-mercaptopropionic acid)

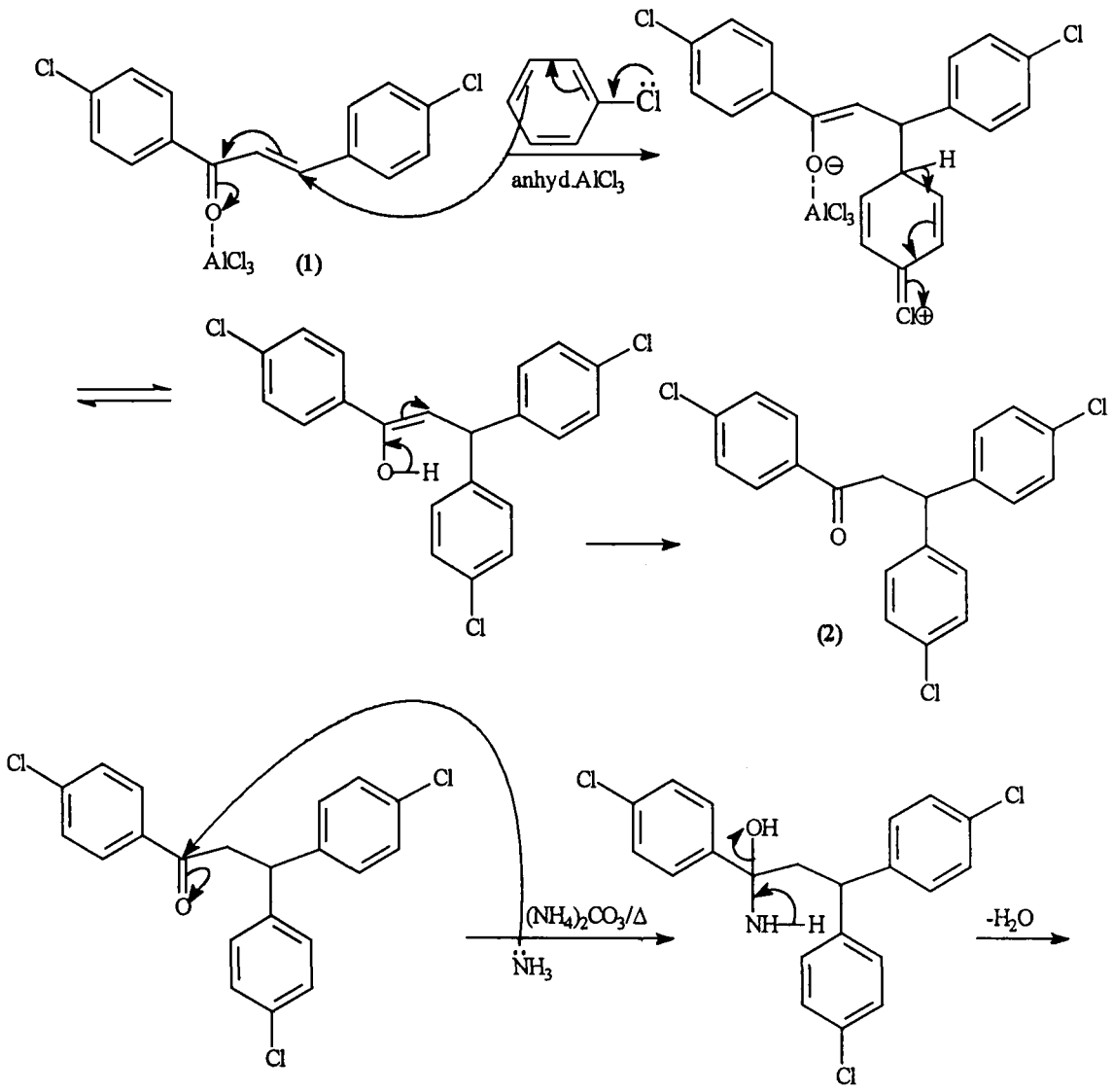


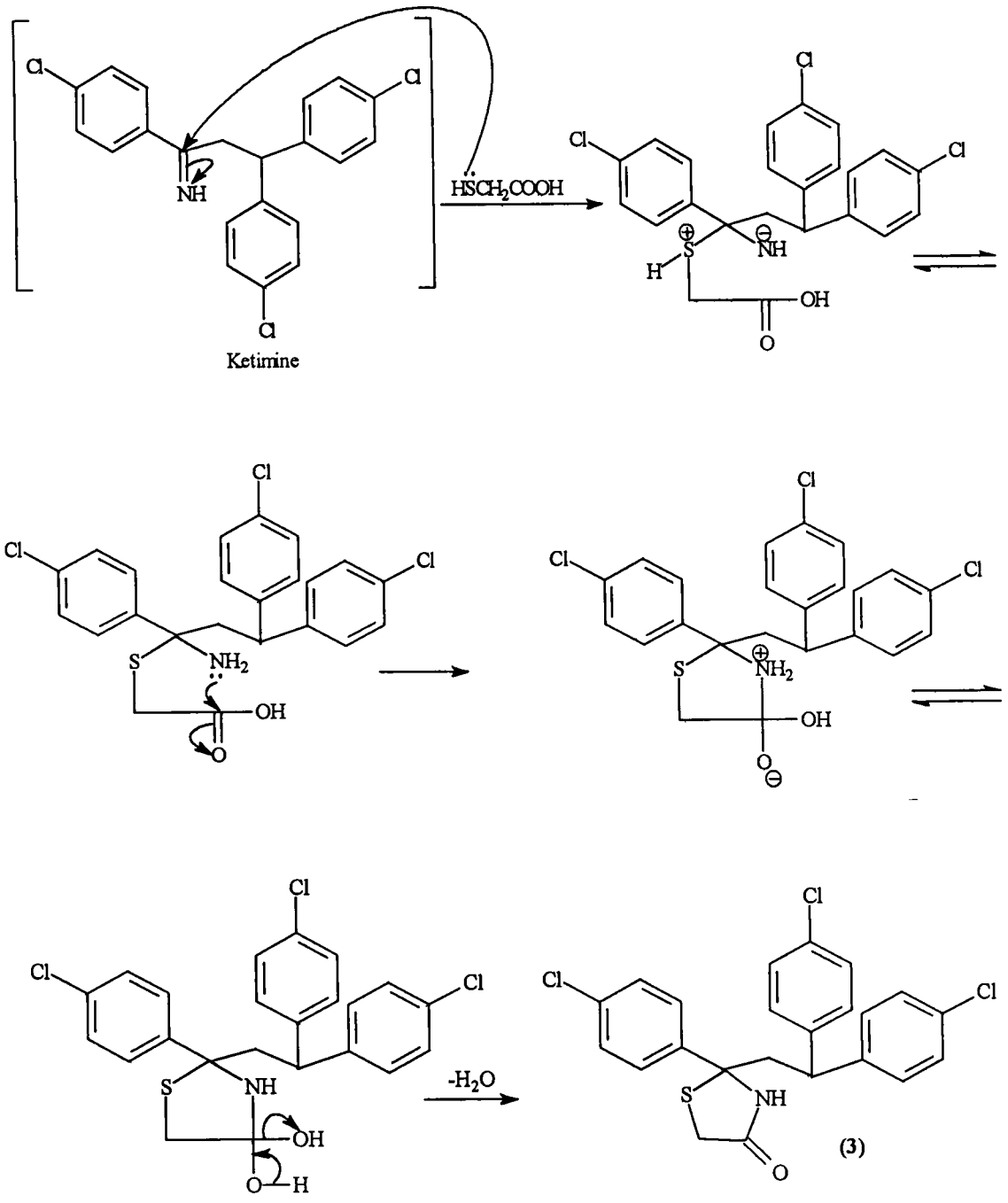
3) $R_1 = H, R_2 = Cl, R_3 = H \quad n_1 = 0$
6) $R_1 = R_2 = OMe, R_3 = H \quad n_1 = 1$
7) $R_1 = R_2 = OMe, R_3 = Me \quad n_1 = 1$
10) $R_1 = H, R_2 = Cl, R_3 = Me \quad n_1 = 1$

SCHEME-I

Mechanism of the above reaction

A plausible mechanism for the above reaction may be offered (**SCHEME-II**). It is believed that the adduct first formed by the nucleophilic addition of chlorobenzene to α, β-unsaturated enone function, reacts with ammonia from ammonium carbonate to give the ketimine intermediate[74]. The reaction then proceeds by the neucleophilic attack of thiol group of HS-CHCOOH upon > C=N, adding to the carbon atom followed by capture
|
R_3
of a proton by nitrogen atom and subsequent cyclization with the elimination of a water molecule. The proposed mechanism is depicted taking an example, the enone (1) as shown in **SCHEME-II**.



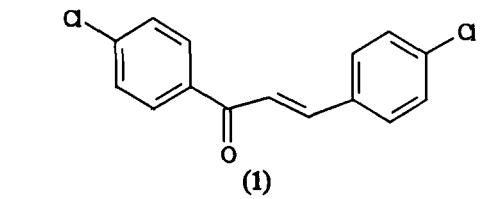


SCHEME-II

Synthesis of 2-[2,2-bis(4-chlorophenyl)ethyl]-2-(4-chlorophenyl)-thiazolidin-4-one E_{1A} (3) from 4,4'-dichlorochalcone (1) via 1,3,3-tris(4-chlorophenyl)propan-1-one P (2) using thioglycollic acid in the presence of ammonium carbonate in dry benzene.

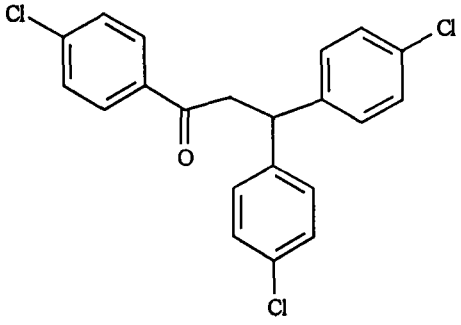
The compound (2) was first prepared by adding an excess of chlorobenzene to a suspension of 4,4'-dichlorochalcone(1) and anhydrous aluminium chloride (molar ratio, 1:3) in chlorobenzene, stirring the reaction mixture for 2.5 h at room temperature. After the reaction was over, the reaction mixture on TLC examination (silica gel 'G', pet. ether (40-60°)-benzene, 9:1 v/v) showed the presence of only one spot, labelled as **P**. On usual work up and crystallisation from benzene, it yielded **P** as white crystalline needles in 66% yield. The adduct (2) was then condensed with mercaptoacetic acid and ammonium carbonate (molar ratio, 1:1.30 : 5.25). The cyclocondensation was carried out by refluxing the reaction mixture in dry benzene for 40 h with azeotropic removal of water. TLC examination (silica gel 'G', pet. ether (40-60°) - diethylether, 7:3 v/v) of the reaction mixture showed the presence of one spot, labelled as E_{1A}. After usual work up and purification of the products by column chromatography over silica gel using pet. ether-diethyl ether (7:3 v/v) as eluent followed by crystallisation (benzene-acetone, 9:1 v/v) afforded E_{1A} (3) as white crystalline globules in 58.6% yield.

The outline of synthesis is given below :



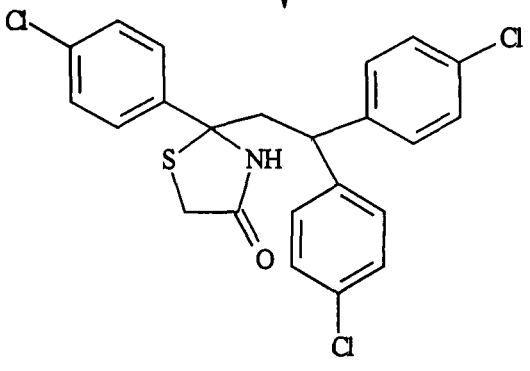
(1)

PhCl/anhydrous $AlCl_3$ (molar ratio, 1:large excess[122] : 3), stirred at r.t., 2.5 h.



P (2)

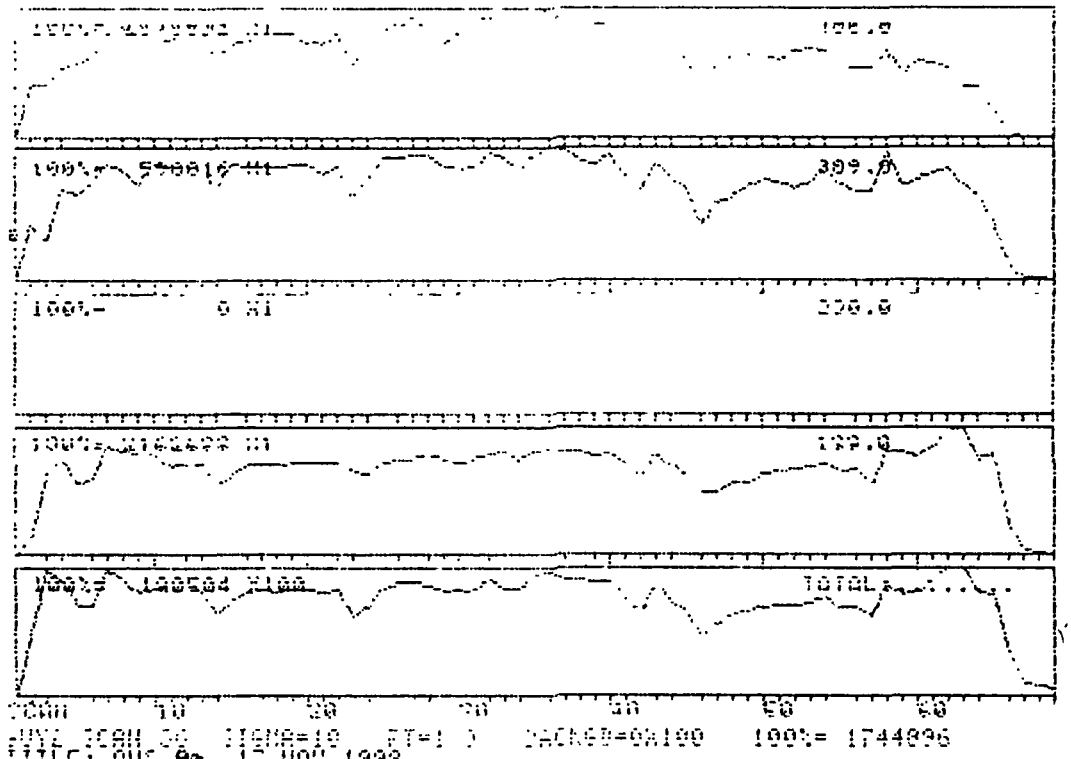
$HSCH_2COOH/(NH_4)_2CO_3$ (molar ratio, 1:1.30:5.25), dry benzene, reflux, 40 h.



E_{1A} (3)

Structure Elucidation of P (2)

It is a white needles shaped crystalline solid, m.p. 155°C and appears light brown on exposure to iodine vapours (TLC). The structure of **P** has been established by FT-IR, DCI-MS, HRMS, ^{1}H-NMR and ^{13}C-NMR spectra. IR spectrum (KBr pellets) of **P** showed characteristic signals at 1677 (C=O), 2927 (CH), 1590 (Phenyl), 1485, 1400, 1264, 1209, 1090, 1013, 838, 774 cm^{-1}. The DCI-MS (NH_3 as reagent gas) spectrum **(FIG. 1)** of **P (2)** showed a set of $[M+NH_4]^+$ peaks at m/z 406/408/410/412 (93.4/97.1/37.5/ 6.8) and an another set of $[M+H]^+$ peaks at m/z 389/391/393/395 (34.2/35.2/ 14.0/2.5), confirming its molecular weight as 388/390/392/394. This is equal to the sum of the molecular weights of *4,4'-dichlorochalcone* (276) and chlorobenzene (112) indicating that the formation of adduct **P (2)** has occurred by the addition of chlorobenzene to α, β-unsaturated enone of the chalcone. The set of peaks at m/z 139/141 (100.0/38.0) appeared as base peak was arised by the cleavage of 1-2 bond while the other set of peaks at m/z 235/237/239 (81.6/605/124) was obtained by the cleavage of 2-3 bond of the adduct molecule as shown in **CHART-1**. The HRMS (ESI) spectrum showed peaks corresponding with $C_{21}H_{15}OCl_3$ [M+Na], which has been calculated as 411.0086 and found to be 411.0089, further confirming its molecular weight 388/390/392/394. The ^{1}H-NMR **(FIG. 2)** and ^{13}C-NMR **(FIG. 3a, 3b)** spectra of **P** dissolved in acetone-d_6 showed signals as assigned **(TABLE-1)**. The assignments of all ^{1}H-NMR and ^{13}C-NMR signals to individual H- and C-atoms have been performed on the basis of typical chemical shift values, multiplicity and relative integrations. The ^{1}H-NMR spectrum of **P** showed a doublet at δ3.92 (J=7.32Hz) and a triplet at δ4.78 (J=7.32Hz) which were attributed to two methylene protons at C-2 and a methine proton at C-3. The signals for aromatic protons appeared as



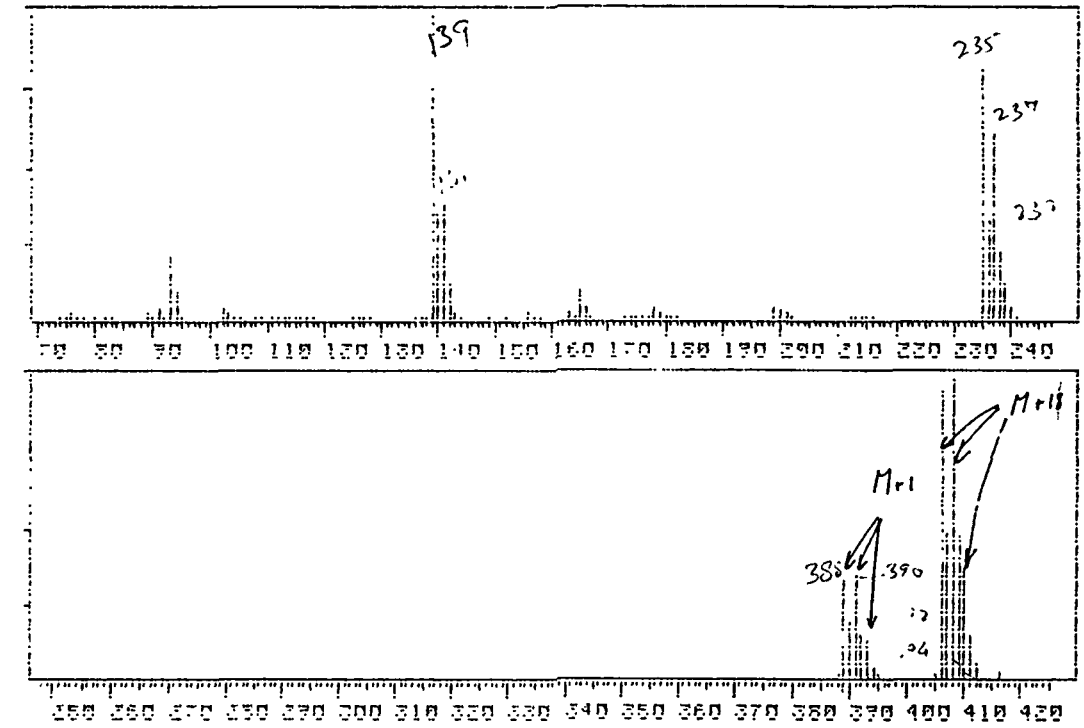


FIG. 1

.	93.00	21	S	.	165.00	11	Z	389.00	34.2	.	407.00	48.3
.	94.00	8	?	.	223.00	01	!	390.00	19.9	.	408.00	97.1
✓	139.00	100	9		236.00	33	5	391.00	35.2	.	409.00	47.8
.	✓140.00	74	?		✓237.00	68	E	392.00	17.8	.	410.00	37.5
.	✓141.00	38	0		238.00	22	V	393.00	14.0	.	411.00	16.1
	✓142.00	13	1		✓239.00	17	A	406.00	93.4	.	412.00	6.0

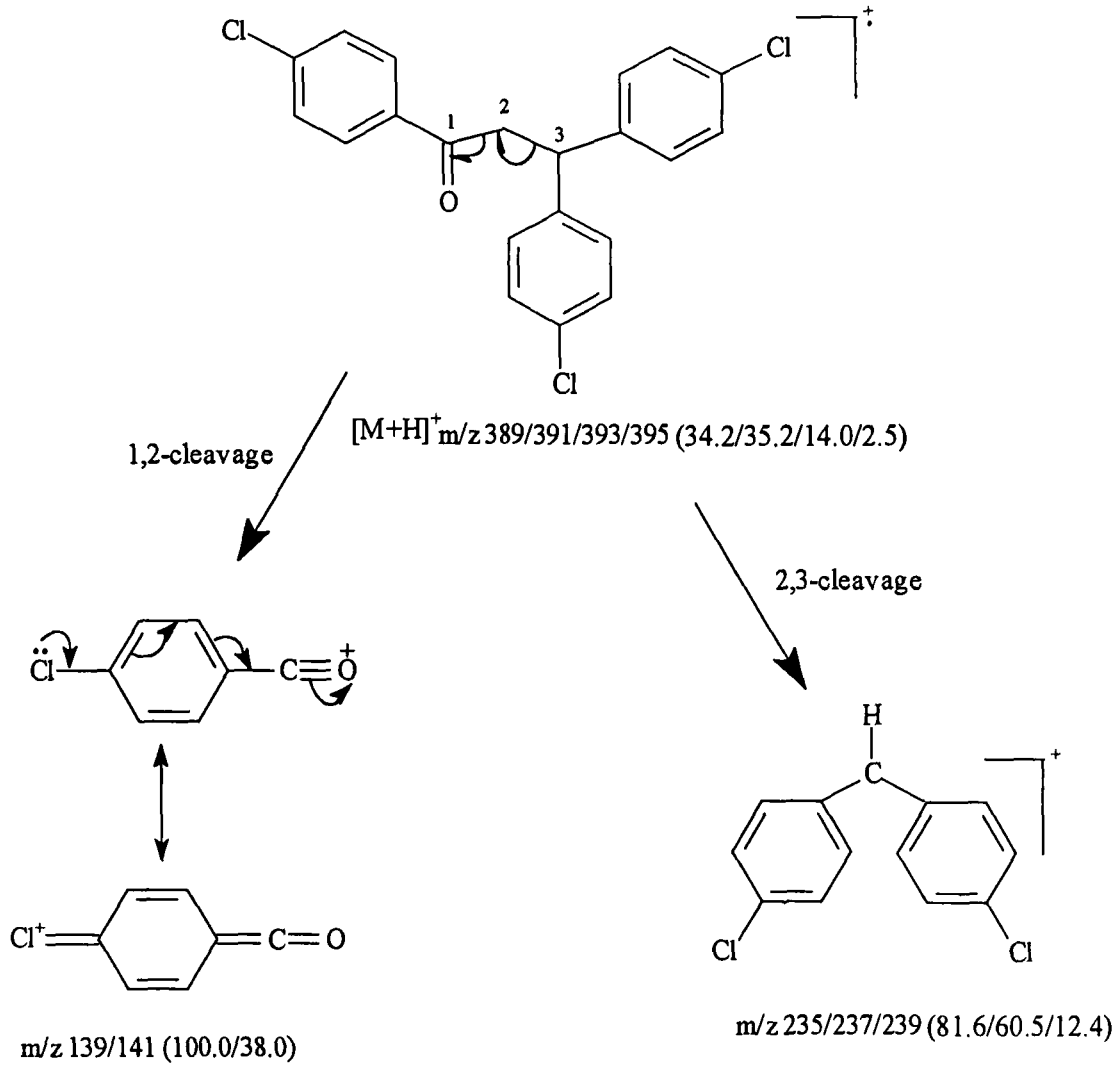


CHART - 1

A_2B_2 pattern and were assigned for three aromatic rings as shown in **TABLE-1**. The ^{13}C-NMR spectrum also showed signals which support the adduct structure.

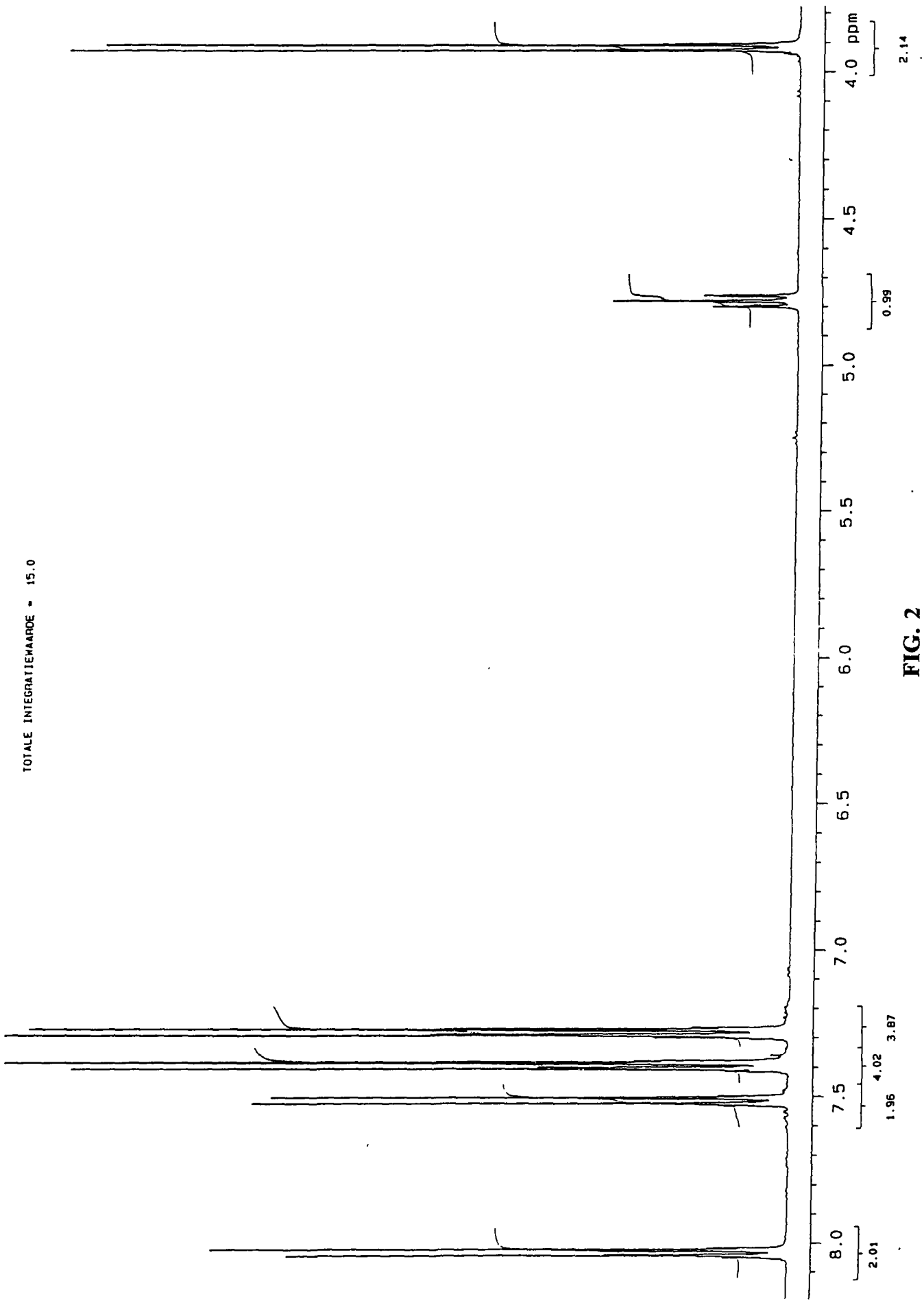

TOTALE INTEGRATIEWAARDE = 15.0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0 ppm
2.01
1.96
4.02
3.87
0.99
2.14

FIG. 2

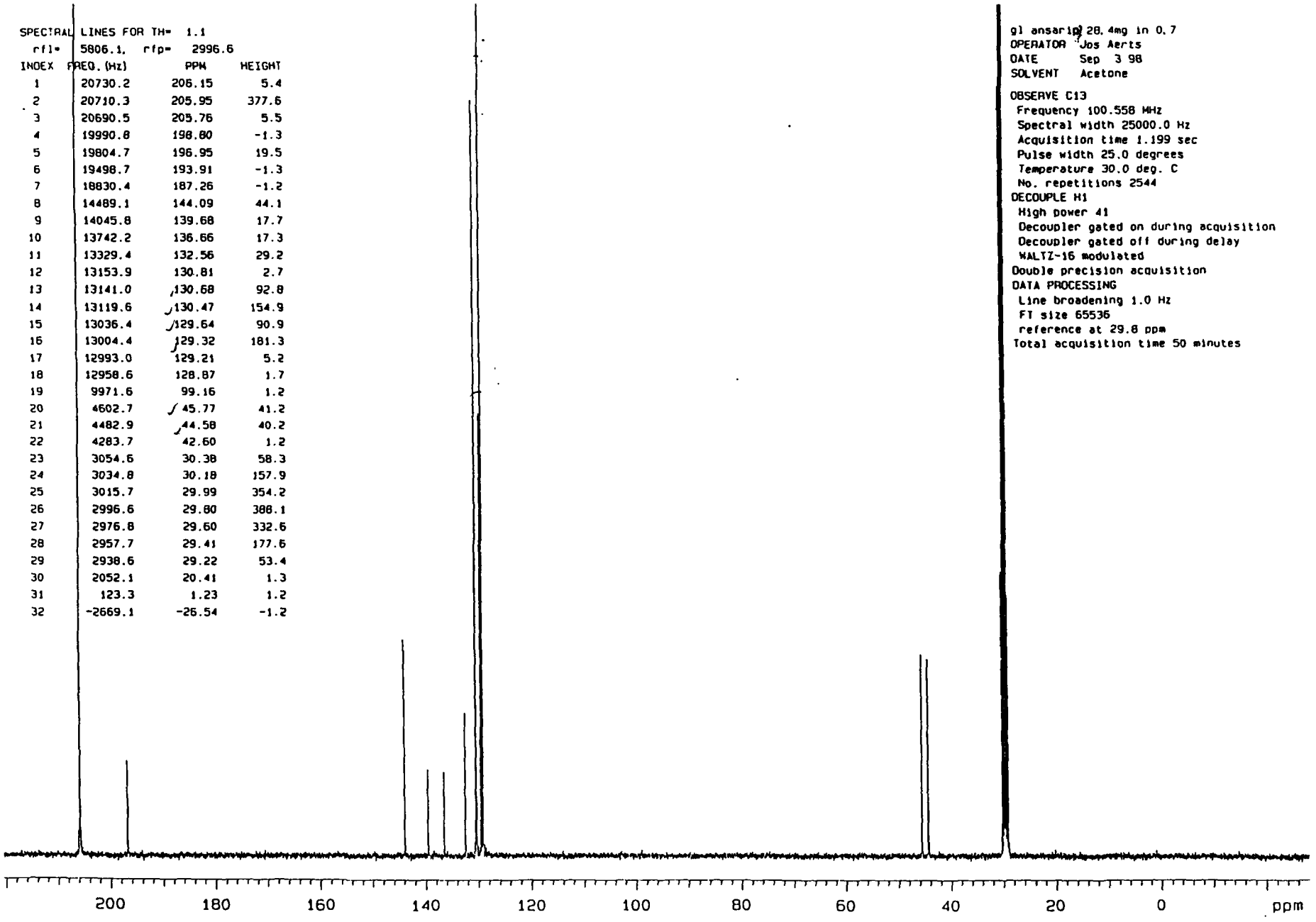

SPECTRAL LINES FOR TH= 1.1
rfl= 5806.1, rfp= 2996.6
INDEX FREQ.(Hz) PPM HEIGHT
1 20730.2 206.15 5.4
2 20710.3 205.95 377.6
3 20690.5 205.76 5.5
4 19990.8 198.80 -1.3
5 19804.7 196.95 19.5
6 19498.7 193.91 -1.3
7 18830.4 187.26 -1.2
8 14489.1 144.09 44.1
9 14045.8 139.68 17.7
10 13742.2 136.66 17.3
11 13329.4 132.56 29.2
12 13153.9 130.81 2.7
13 13141.0 130.68 92.8
14 13119.6 130.47 154.9
15 13036.4 129.64 90.9
16 13004.4 129.32 181.3
17 12993.0 129.21 5.2
18 12958.6 128.87 1.7
19 9971.6 99.16 1.2
20 4602.7 45.77 41.2
21 4482.9 44.58 40.2
22 4283.7 42.60 1.2
23 3054.6 30.38 58.3
24 3034.8 30.18 157.9
25 3015.7 29.99 354.2
26 2996.6 29.80 388.1
27 2976.8 29.60 332.6
28 2957.7 29.41 177.6
29 2938.6 29.22 53.4
30 2052.1 20.41 1.3
31 123.3 1.23 1.2
32 -2669.1 -26.54 -1.2
gl ansarip 28.4mg in 0.7
OPERATOR Jos Aerts
DATE Sep 3 98
SOLVENT Acetone
OBSERVE C13
Frequency 100.558 MHz
Spectral width 25000.0 Hz
Acquisition time 1.199 sec
Pulse width 25.0 degrees
Temperature 30.0 deg. C
No. repetitions 2544
DECOUPLE H1
High power 41
Decoupler gated on during acquisition
Decoupler gated off during delay
WALTZ-16 modulated
Double precision acquisition
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
reference at 29.8 ppm
Total acquisition time 50 minutes
200
180
160
140
120
100
80
60
40
20
0
ppm

FIG. 3a

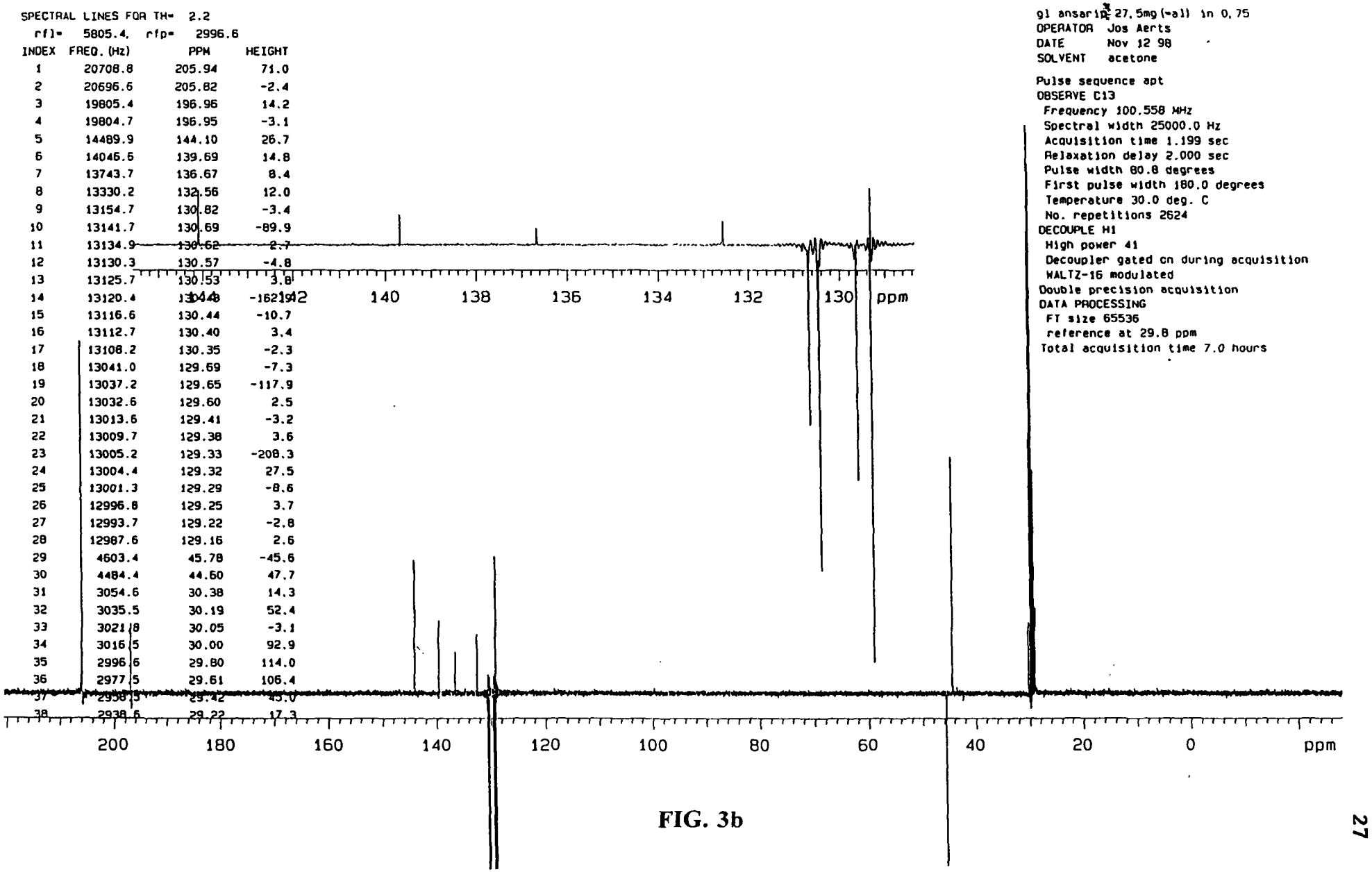
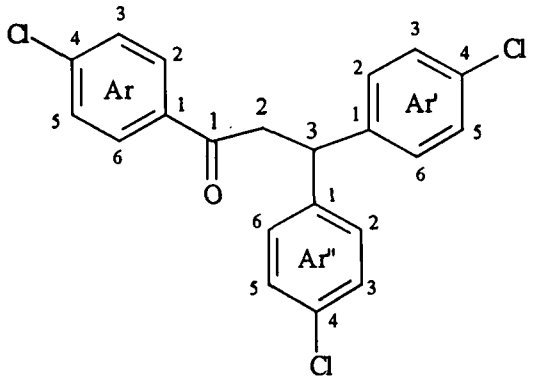

SPECTRAL LINES FOR TH= 2.2
rfl= 5805.4, rfp= 2996.6
INDEX FREQ.(Hz) PPM HEIGHT
1 20708.8 205.94 71.0
2 20696.6 205.82 -2.4
3 19805.4 196.96 14.2
4 19804.7 196.95 -3.1
5 14489.9 144.10 26.7
6 14046.5 139.69 14.8
7 13743.7 136.67 8.4
8 13330.2 132.56 12.0
9 13154.7 130.82 -3.4
10 13141.7 130.69 -89.9
11 13134.9 130.62 2.7
12 13130.3 130.57 -4.8
13 13125.7 130.53 3.8
14 13120.4 130.48 -162.9
15 13116.6 130.44 -10.7
16 13112.7 130.40 3.4
17 13108.2 130.35 -2.3
18 13041.0 129.69 -7.3
19 13037.2 129.65 -117.9
20 13032.6 129.60 2.5
21 13013.6 129.41 -3.2
22 13009.7 129.38 3.6
23 13005.2 129.33 -208.3
24 13004.4 129.32 27.5
25 13001.3 129.29 -8.6
26 12996.8 129.25 3.7
27 12993.7 129.22 -2.8
28 12987.6 129.16 2.6
29 4603.4 45.78 -45.6
30 4484.4 44.60 47.7
31 3054.6 30.38 14.3
32 3035.5 30.19 52.4
33 3021.8 30.05 -3.1
34 3016.5 30.00 92.9
35 2996.6 29.80 114.0
36 2977.5 29.61 106.4
37 2958.5 29.42 45.0
38 2938.6 29.22 17.3
142
140
138
136
134
132
130
ppm
200
180
160
140
120
100
80
60
40
20
0
ppm
gl ansari 27.5mg (=al) in 0.75
OPERATOR Jos Aerts
DATE Nov 12 98
SOLVENT acetone
Pulse sequence apt
OBSERVE C13
Frequency 100.558 MHz
Spectral width 25000.0 Hz
Acquisition time 1.199 sec
Relaxation delay 2.000 sec
Pulse width 80.8 degrees
First pulse width 180.0 degrees
Temperature 30.0 deg. C
No. repetitions 2624
DECOUPLE H1
High power 41
Decoupler gated on during acquisition
WALTZ-16 modulated
Double precision acquisition
DATA PROCESSING
FT size 65536
reference at 29.8 ppm
Total acquisition time 7.0 hours

FIG. 3b

TABLE -1 : ^{1}H-NMR and ^{13}C-NMR spectral data of P (2)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)	C-nr	δ (ppm)	INEPT
2	3.92	2H	d	$J_{2,3}$ = 7.32	1	196.95	C
3	4.78	1H	t	$J_{2,3}$ = 7.32	2	44.58	CH_2
Ar-2,6	8.04	2H	d	$J_{Ar\text{-}2,6,\ Ar\text{-}3,5}$ = 8.69	3	45.77	CH
Ar-3,5	7.51	2H	d	$J_{Ar\text{-}2,6,\ Ar\text{-}3,5}$ = 8.69	Ar-1	136.66	C
2xAr'-2,6	7.28	4H	d	$J_{Ar'/Ar'\text{-}2,6,Ar'/Ar'\text{-}3,5}$=8.69	Ar-2,6	130.68	CH
2xAr'-3,5	7.39	4H	d	$J_{Ar'/Ar'\text{-}2,6,Ar'/Ar'\text{-}3,5}$=8.69	Ar-3,5	129.64	CH
					Ar-4	139.68	C
					Ar'/Ar'-1	144.09	C
					Ar'/Ar'-2,6	130.47	CH
					Ar'/Ar'3,5	129.32	CH
					Ar'/Ar'-4	132.56	C

On the basis of these facts, the structure of **P** was formulated as *1,3,3-tris(4-chlorophenyl)propan-1-one(2)*.



P (2)

Structure Elucidation of E_{1A} (3)

It is a white crystalline globules solid, m.p. 170 °C and appears reddish brown on exposure to iodine vapours (TLC). The structure of E_{1A} has been established by FT-IR, DCI-MS, ^{1}H-NMR and ^{13}C-NMR, INEPT, COSY, HETCOR, LONG RANGE HETCOR and NOE spectra. IR spectrum (KBr) of E_{1A} showed characteristic absorption bands at 3380 (NH), 1665 (-CONH), 1600, 1590 (phenyl), 1470(S-CH_2), 1405(C-H), 1250, 1080, 1010, 825 cm^{-1}. The DCI-MS (NH_3 as reagent gas) spectrum **(FIG. 4)** of E_{1A} showed a set of $[M+NH_4]^+$ peaks at m/z 479/481/483/485 (21.0/22.7/10.0/4.4) and an another set of $[M+H]^+$ peaks at m/z 462/464/466/468 (89.6/100.0/44.8/8.8) as the base peak, confirming its molecular weight 461/463/465/467. This is equal to the sum of the molecular weights of **P (2)** (388), thioglycollic acid (92) and ammonia (17) minus two molecules of water (36) which indicated the formation of thiazolidinone ring by the cyclocondensation of **P (2)** with thioglycollic acid and ammonia. The HRMS (ESI) spectrum showed molecular

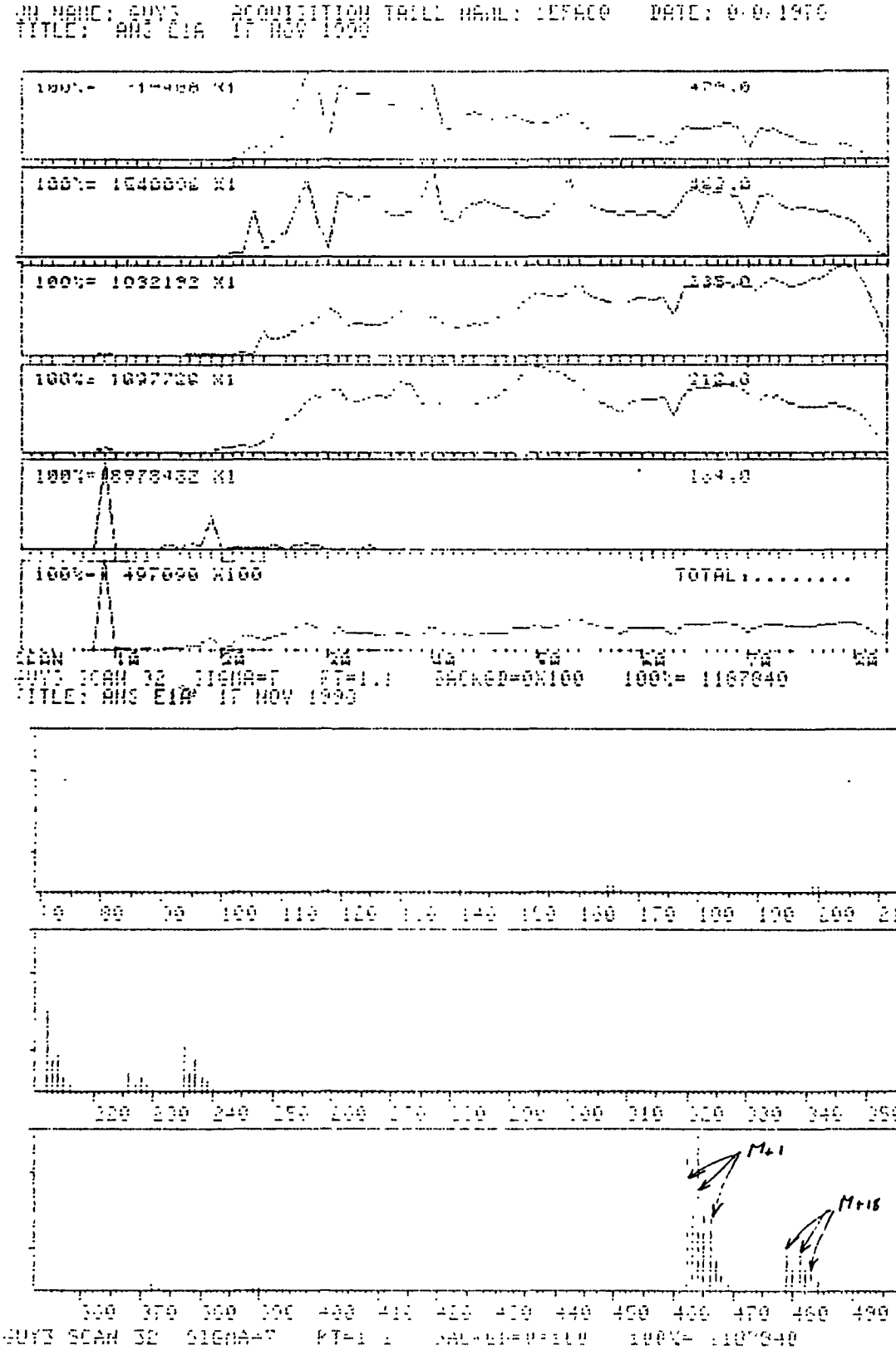

TITLE: AMS EIA 17 NOV 1993
100%= 1032192 X1
100%= 1097728 X1
100%= 497090 X100
TOTAL.....
TITLE: AMS EIA 17 NOV 1993
M+1
M+18

FIG. 4

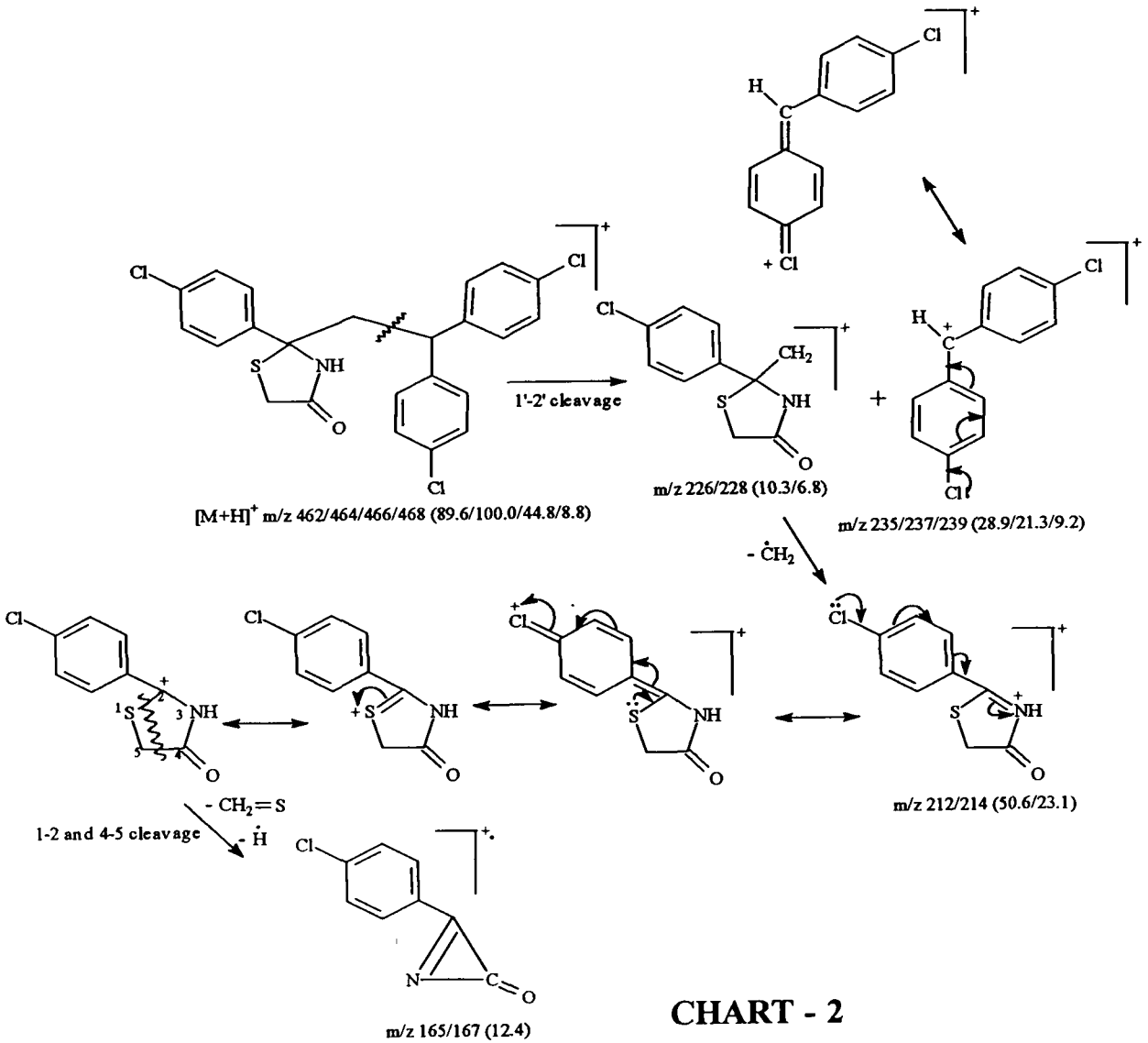

1'-2' cleavage
[M+H]+ m/z 462/464/466/468 (89.6/100.0/44.8/8.8)
m/z 226/228 (10.3/6.8)
m/z 235/237/239 (28.9/21.3/9.2)
- ĊH2
m/z 212/214 (50.6/23.1)
- CH2=S
1-2 and 4-5 cleavage
- Ḣ
m/z 165/167 (12.4)

CHART - 2

ion which is corresponding with the molecular formula $C_{23}H_{18}Cl_3NOS$ $[M+H]^+$, calculated 462.0253 and found 462.0264; further confirming its molecular weight 461/463/465/467. The main fragment ion peaks observed at m/z 212/214 (50.6/23.1) $[p\text{-}ClC_6H_4C_3H_3ONS]^+$ was arised by the cleavage at α-position to the heterocyclic ring on the alkyl chain side, showing the location of the ring. The mode of fragmentations is shown in **CHART - 2**. The ^{1}H-NMR **(FIG. 5)** and ^{13}C-NMR **(FIG. 6a, 6b)** spectra of $\mathbf{E_{1A}}$ dissolved in acetone-d_6 showed signals as assigned **(TABLES-2 and 3)**. The assignments of all ^{1}H-NMR and ^{13}C-NMR signals to specific H- and C-atoms have been performed on the basis of typical chemical shift values, multiplicity and relative integrations. The ^{1}H-NMR spectrum showed a singlet at δ8.04 for NH proton and two geminal doublets at δ3.45, 3.56 (J=15.42) for the ring methylene protons ($-CH_2-S-$), suggesting the formation of thiazolidinone ring. The formation of thiazolidinone ring was also supported by a shift of C-2 proton of **P (2)** to higher field from δ3.92 to 3.05-3.16 (position 1' in $\mathbf{E_{1A}}$). The ^{13}C-NMR spectrum is also in agreement with thiazolidinone ring as C-1 signal of the compound **P(2)** has shifted to higher field from δ196.95 to δ70.84 in $\mathbf{E_{1A}}$ due to disappearance of C=O group and formation of the ring. The aromatic protons signals appeared as A_2B_2 system as in compound **P (2)**. On the basis of these evidence, the structure of $\mathbf{E_{1A}}$ has been formulated as *2-[2,2-bis(4-chlorophenyl)ethyl]-2-(4-chlorophenyl)thiazolidin-4-one* ***(3)***. The structure and stereochemistry of compound $\mathbf{E_{1A}}$ **(3)** have further been confirmed by additional NMR techniques such as COSY, INEPT, HETCOR, LONG RANGE HETCOR and 2D-NOE spectra **(FIGS. 7a-c, 8a-b, 9a-c and 10a-d)**. These spectra suggested that the relative configuration of the product **(3)** is most probably μ (unlike[118]) and partial conformation of both central bonds C-2-C-1' and C-1'-C-2' as antiperiplanar **(FIG. 1)**[119,120]. Especially,

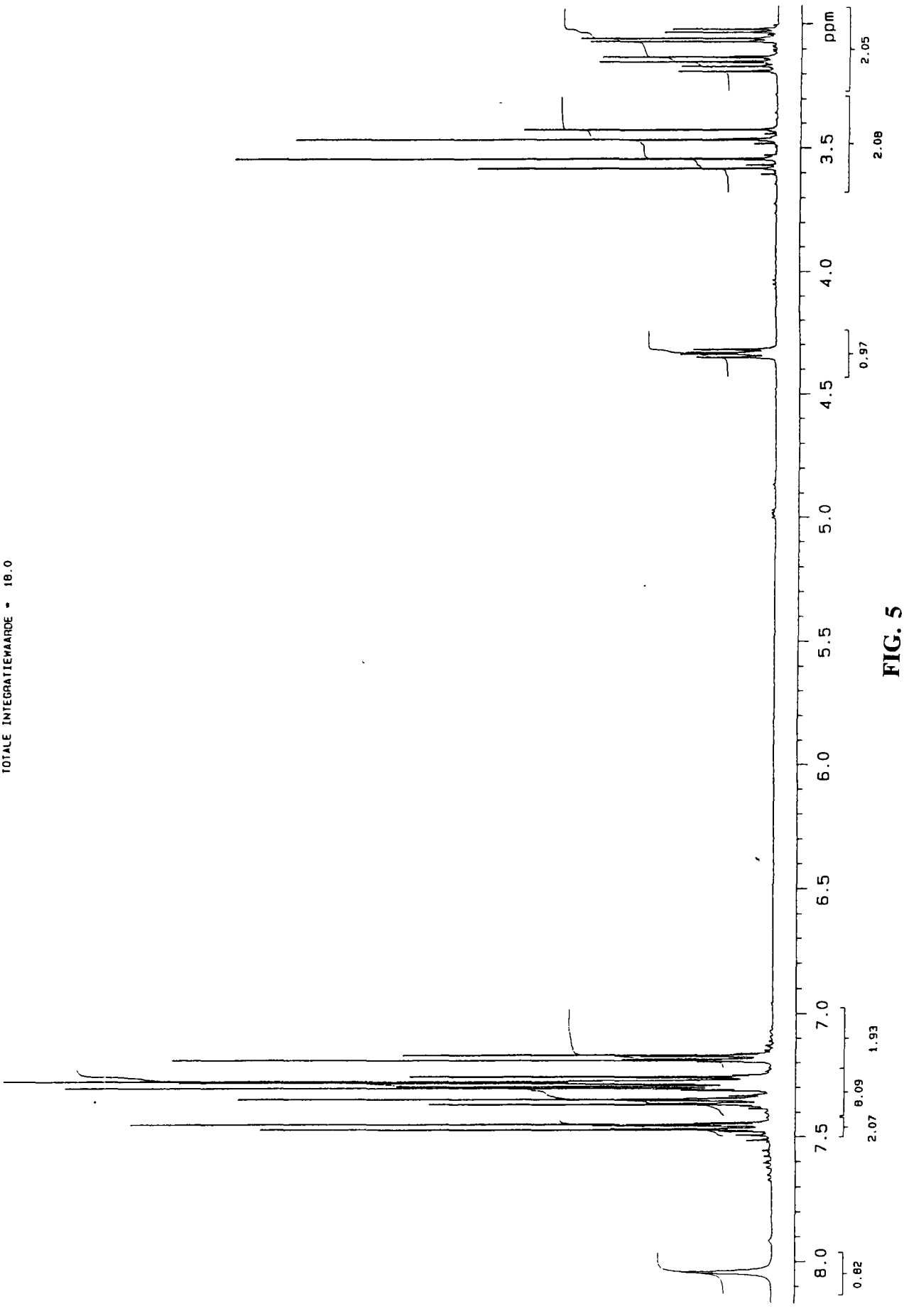
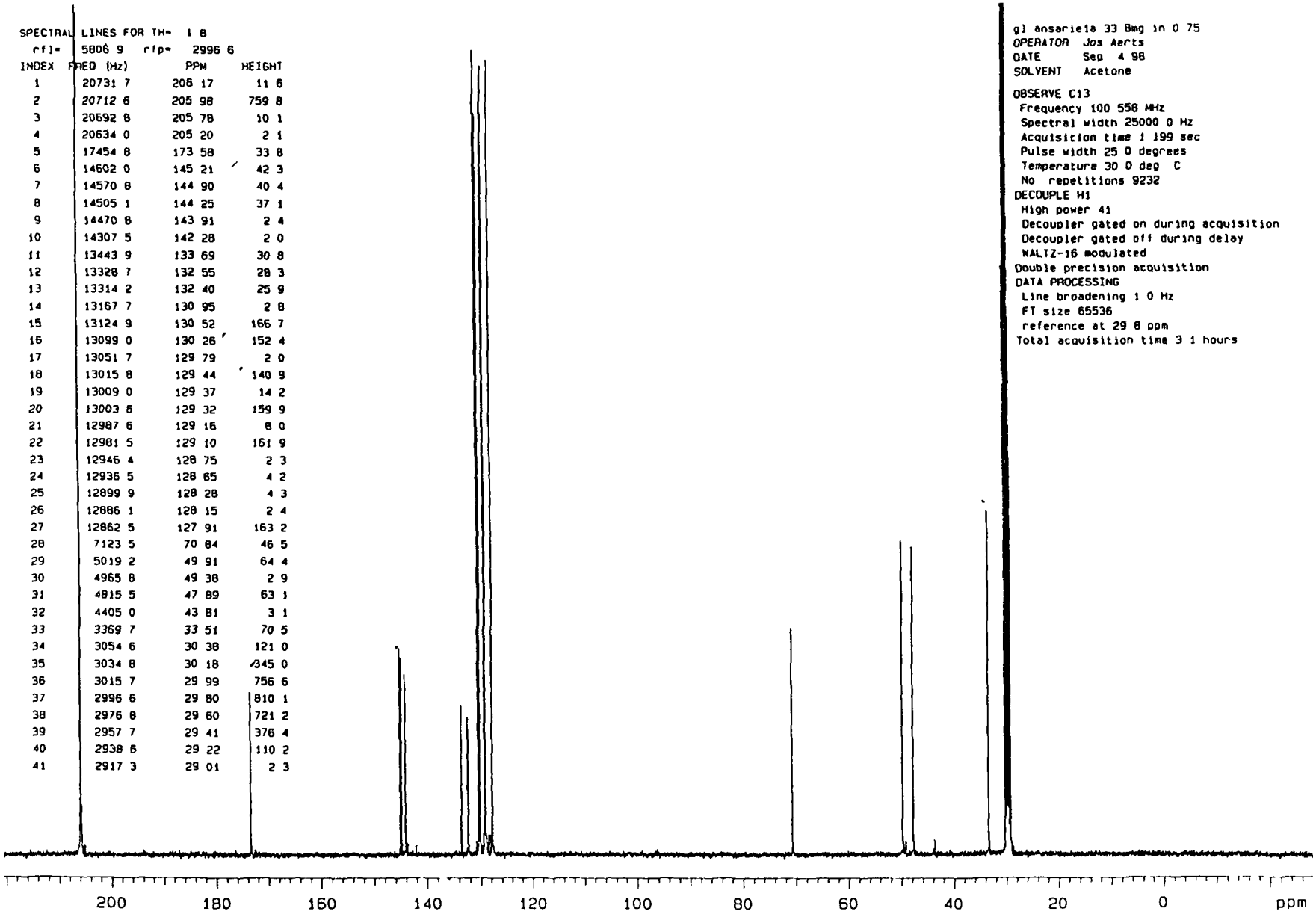

TOTALE INTEGRATIEWAARDE = 18.0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
0.82
2.07
8.09
1.93
0.97
2.08
2.05

FIG. 5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rfl= 5806 9 rfp= 2996 6
INDEX FREQ (Hz) PPM HEIGHT
1 20731 7 206 17 11 6
2 20712 6 205 98 759 8
3 20692 8 205 78 10 1
4 20634 0 205 20 2 1
5 17454 8 173 58 33 8
6 14602 0 145 21 42 3
7 14570 8 144 90 40 4
8 14505 1 144 25 37 1
9 14470 8 143 91 2 4
10 14307 5 142 28 2 0
11 13443 9 133 69 30 8
12 13328 7 132 55 28 3
13 13314 2 132 40 25 9
14 13167 7 130 95 2 8
15 13124 9 130 52 166 7
16 13099 0 130 26 152 4
17 13051 7 129 79 2 0
18 13015 8 129 44 140 9
19 13009 0 129 37 14 2
20 13003 6 129 32 159 9
21 12987 6 129 16 8 0
22 12981 5 129 10 161 9
23 12946 4 128 75 2 3
24 12936 5 128 65 4 2
25 12899 9 128 28 4 3
26 12886 1 128 15 2 4
27 12862 5 127 91 163 2
28 7123 5 70 84 46 5
29 5019 2 49 91 64 4
30 4965 8 49 38 2 9
31 4815 5 47 89 63 1
32 4405 0 43 81 3 1
33 3369 7 33 51 70 5
34 3054 6 30 38 121 0
35 3034 8 30 18 345 0
36 3015 7 29 99 756 6
37 2996 6 29 80 810 1
38 2976 8 29 60 721 2
39 2957 7 29 41 376 4
40 2938 6 29 22 110 2
41 2917 3 29 01 2 3
gl ansariela 33 8mg in 0 75
OPERATOR Jos Aerts
DATE Sep 4 98
SOLVENT Acetone
OBSERVE C13
Frequency 100 558 MHz
Spectral width 25000 0 Hz
Acquisition time 1 199 sec
Pulse width 25 0 degrees
Temperature 30 0 deg C
No repetitions 9232
DECOUPLE H1
High power 41
Decoupler gated on during acquisition
Decoupler gated off during delay
WALTZ-16 modulated
Double precision acquisition
DATA PROCESSING
Line broadening 1 0 Hz
FT size 65536
reference at 29 8 ppm
Total acquisition time 3 1 hours
200
180
160
140
120
100
80
60
40
20
0
ppm

FIG. 6a

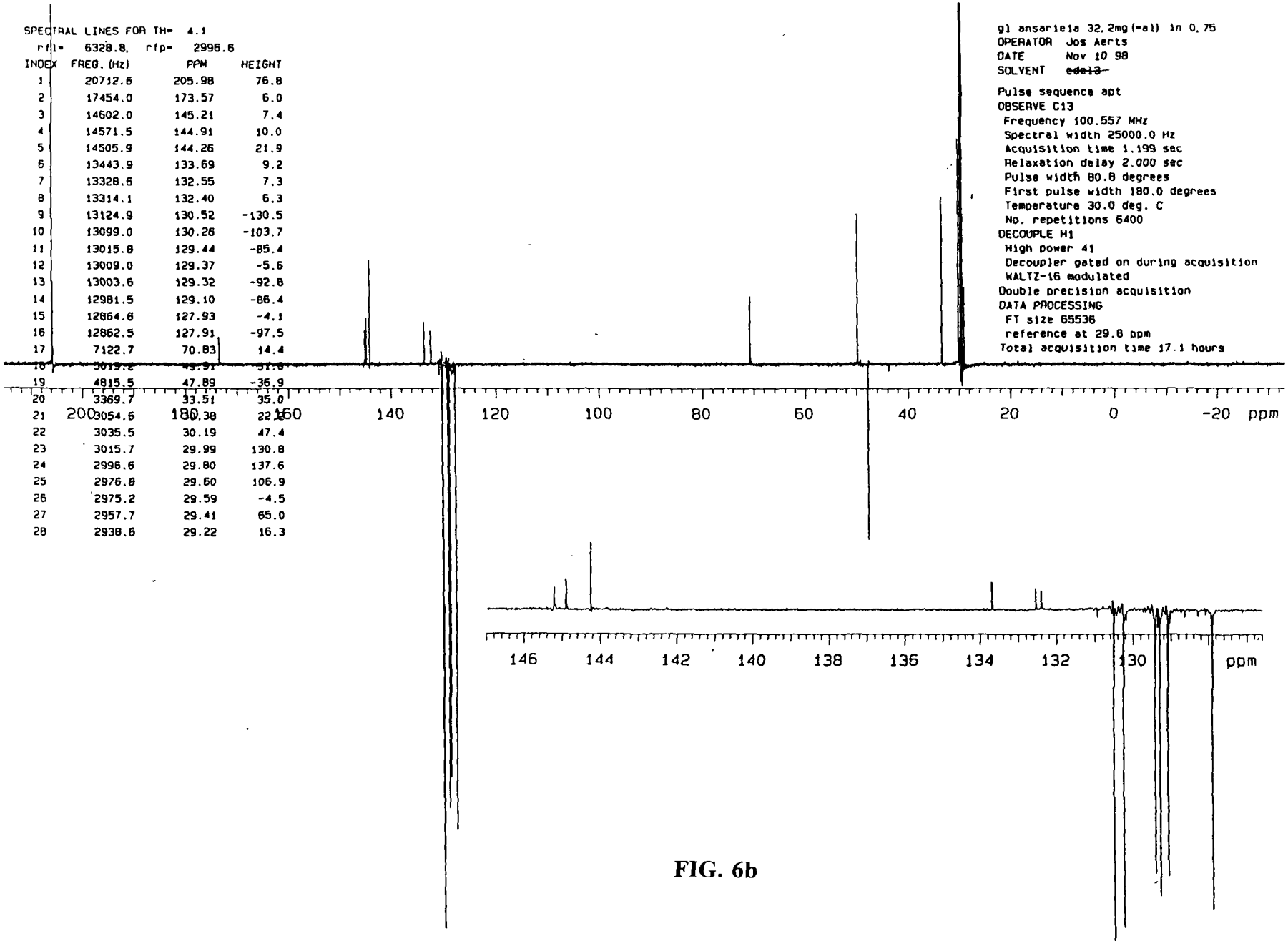
SPECTRAL LINES FOR TH= 4.1
rfl= 6328.8, rfp= 2996.6
INDEX FREQ.(Hz) PPM HEIGHT
1 20712.6 205.98 76.8
2 17454.0 173.57 6.0
3 14602.0 145.21 7.4
4 14571.5 144.91 10.0
5 14505.9 144.26 21.9
6 13443.9 133.69 9.2
7 13328.6 132.55 7.3
8 13314.1 132.40 6.3
9 13124.9 130.52 -130.5
10 13099.0 130.26 -103.7
11 13015.8 129.44 -85.4
12 13009.0 129.37 -5.6
13 13003.6 129.32 -92.8
14 12981.5 129.10 -86.4
15 12864.8 127.93 -4.1
16 12862.5 127.91 -97.5
17 7122.7 70.83 14.4
19 4815.5 47.89 -36.9
20 3369.7 33.51 35.0
21 3054.6 30.38 22.6
22 3035.5 30.19 47.4
23 3015.7 29.99 130.8
24 2996.6 29.80 137.6
25 2976.8 29.60 106.9
26 2975.2 29.59 -4.5
27 2957.7 29.41 65.0
28 2938.6 29.22 16.3
gl ansariela 32.2mg(=al) in 0.75
OPERATOR Jos Aerts
DATE Nov 10 98
SOLVENT cdcl3
Pulse sequence apt
OBSERVE C13
Frequency 100.557 MHz
Spectral width 25000.0 Hz
Acquisition time 1.199 sec
Relaxation delay 2.000 sec
Pulse width 80.8 degrees
First pulse width 180.0 degrees
Temperature 30.0 deg. C
No. repetitions 6400
DECOUPLE H1
High power 41
Decoupler gated on during acquisition
WALTZ-16 modulated
Double precision acquisition
DATA PROCESSING
FT size 65536
reference at 29.8 ppm
Total acquisition time 17.1 hours
200
180
160
140
120
100
80
60
40
20
0
-20
ppm
146
144
142
140
138
136
134
132
130
ppm

FIG. 6b

TABLE -2 : ^{1}H-NMR spectral data of E_{1A} (3)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)	NOE
5_{up}	3.45	1H	d	$J_{5up,5dn}$ = 15.42	–
5_{dn}	3.56	1H	d	$J_{5up,5dn}$ = 15.42	–
NH	8.04	1H	brs	–	–
$1'_{up}$	3.05	1H	dd	$J_{1'up,1'dn}$ = 14.80; $J_{1'up,2'}$ = 5.03	H-2'; H–Ar-2,6, H–Ar"-2,6
$1'_{dn}$	3.16	1H	dd	$J_{1'up,1'dn}$ = 14.80; $J_{1'dn,2'}$ = 7.78	H-2'; H-Ar'-2,6
2'	4.33	1H	dd	$J_{1'up,2'}$ = 5.03; $J_{1'dn,2'}$ = 7.78	H-$1'_{up}$;H–$1'_{dn}$;H–Ar'-2,6, H–Ar"-2,6
Ar-2,6	7.46	2H	d	$J_{Ar\text{-}2,6,Ar\text{-}3,5}$ = 8.86	H-$1'_{up}$
Ar-3,5	7.31	2H	d	$J_{Ar\text{-}2,6,Ar\text{-}3,5}$ = 8.86	–
Ar'-2,6	7.30	2H	d	$J_{Ar'\text{-}2,6,Ar'\text{-}3,5}$ = 8.40	H-$1'_{dn}$; H-2'
Ar'-3,5	7.20	2H	d	$J_{Ar'\text{-}2,6,Ar'\text{-}3,5}$ = 8.40	–
Ar"-2,6	7.36	2H	d	$J_{Ar"\text{-}2,6,Ar"\text{-}3,5}$ = 8.55	H-$1'_{up}$; H-2'
Ar"-3,5	7.28	2H	d	$J_{Ar"\text{-}2,6,Ar"\text{-}3,5}$ = 8.55	–

TABLE -3 : ^{13}C-NMR spectral data of E_{1A} (3)

C-nr	δ (ppm)	INEPT	Long range HETCOR correlation with
2	70.84	C	H-1'$_{up}$, H-1'$_{dn}$, H-Ar-2,6
4	173.58	C	H-5$_{up}$, H-5$_{dn}$
5	33.51	CH_2	–
1'	49.91	CH_2	H-2'
2'	47.89	CH	H-1'$_{dn}$, H-Ar'-2,6, H-Ar"-2,6
Ar-1	145.21	C	H-Ar-3,5
Ar-2,6	127.91	CH	–
Ar-3,5	129.10	CH	–
Ar-4	133.69[a]	C	–
Ar'-1	144.90[b]	C	–
Ar'-2,6	130.52	CH	H-2'
Ar'-3,5	129.32	CH	–
Ar'-4	132.55[a]	C	–
Ar"-1	144.25[b]	C	–
Ar"-2,6	130.26	CH	H-2'
Ar"-3,5	129.44	CH	–
Ar"-4	132.40[b]	C	–

[a]Assignment may be reversed.
[b]Assignment may be reversed.

STANDARD 1H OBSERVE
COSY
Pulse Sequence: relayh
Solvent: Acetone
Temp. 30.0 C / 303.1 K
UNITY-400 "nmrvarian2000"

PULSE SEQUENCE: relayh
Relax. delay 1.000 sec
COSY 90-90
Acq. time 0.185 sec
Width 2767.8 Hz
2D Width 2767.8 Hz
40 repetitions
144 increments
OBSERVE H1, 399.8725818 MHz
DATA PROCESSING
Sine bell 0.092 sec
F1 DATA PROCESSING
Sine bell 0.026 sec
FT size 4096 x 2048
Total time 1 hr, 57 min, 28 sec

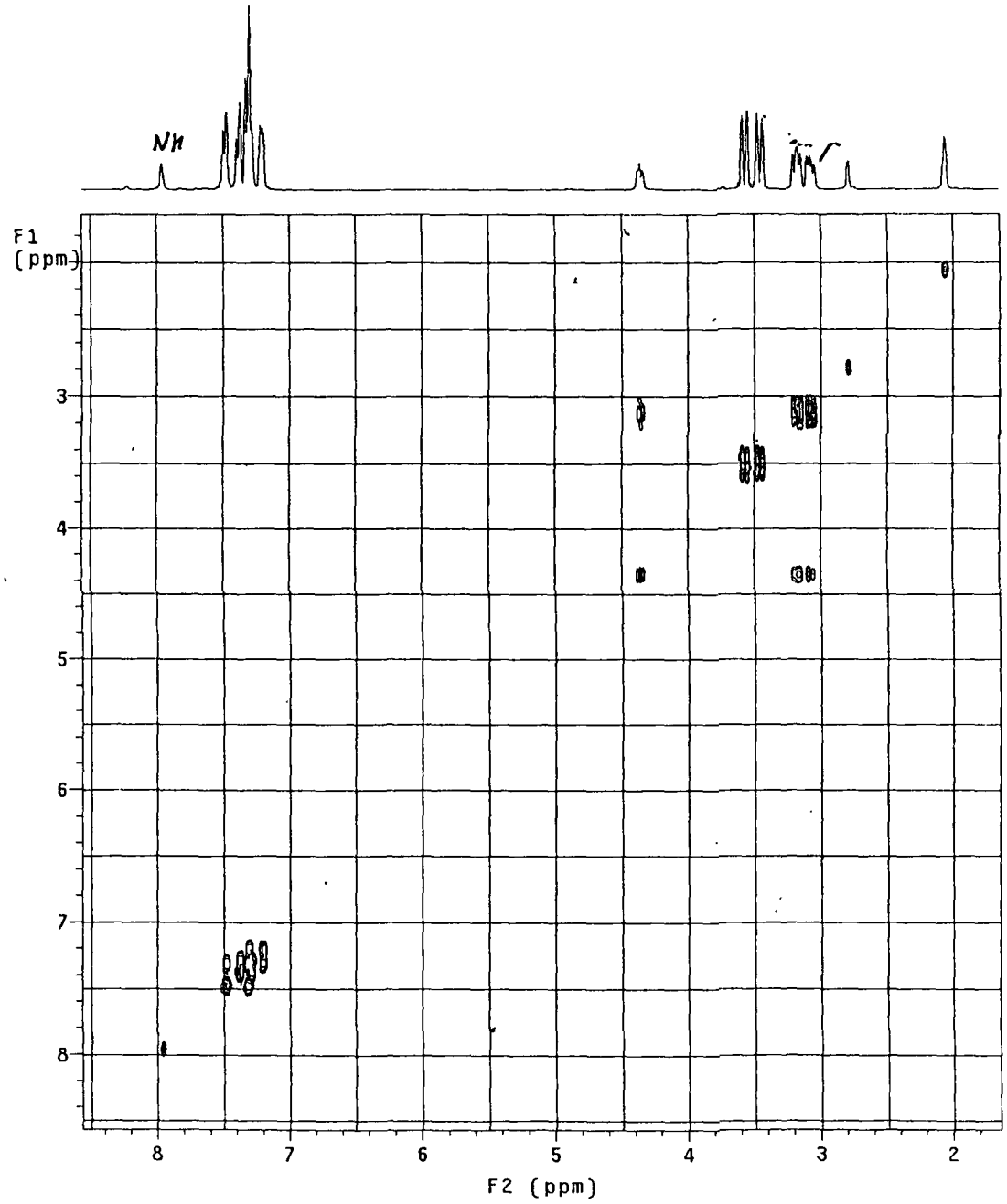

FIG. 7a

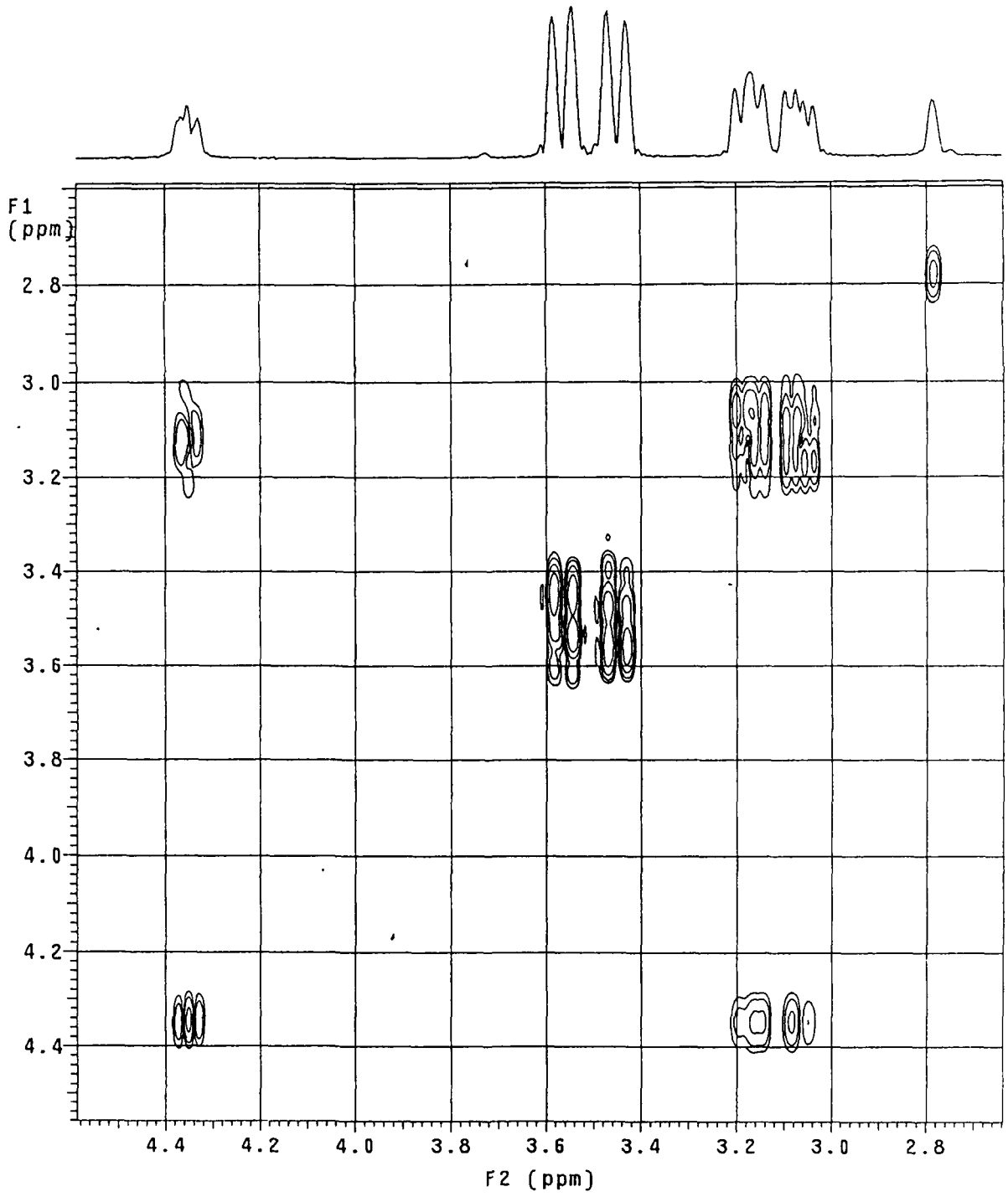

FIG. 7b

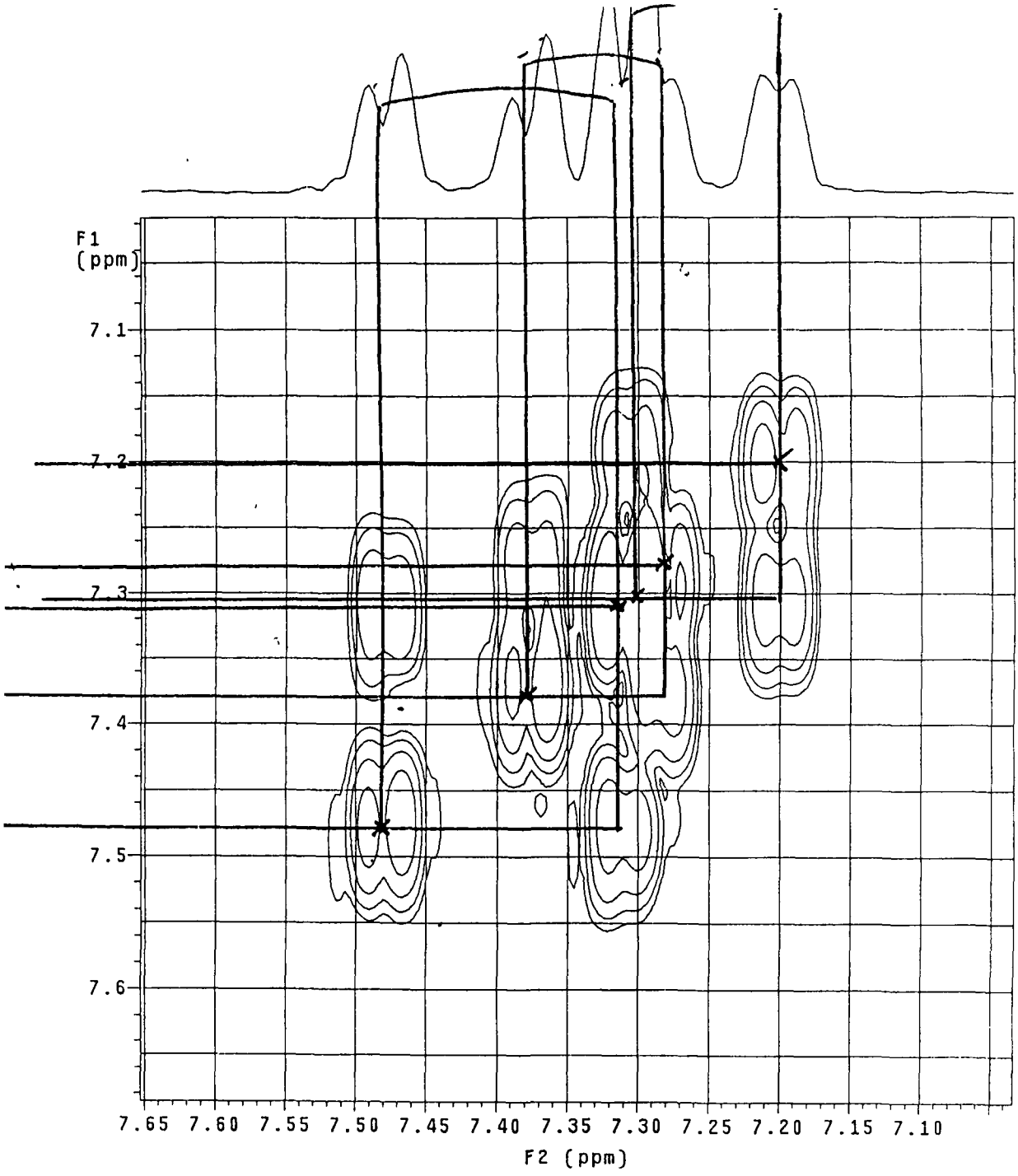
F1
(ppm)
7.1
7.2
7.3
7.4
7.5
7.6
7.65 7.60 7.55 7.50 7.45 7.40 7.35 7.30 7.25 7.20 7.15 7.10
F2 (ppm)

FIG. 7c

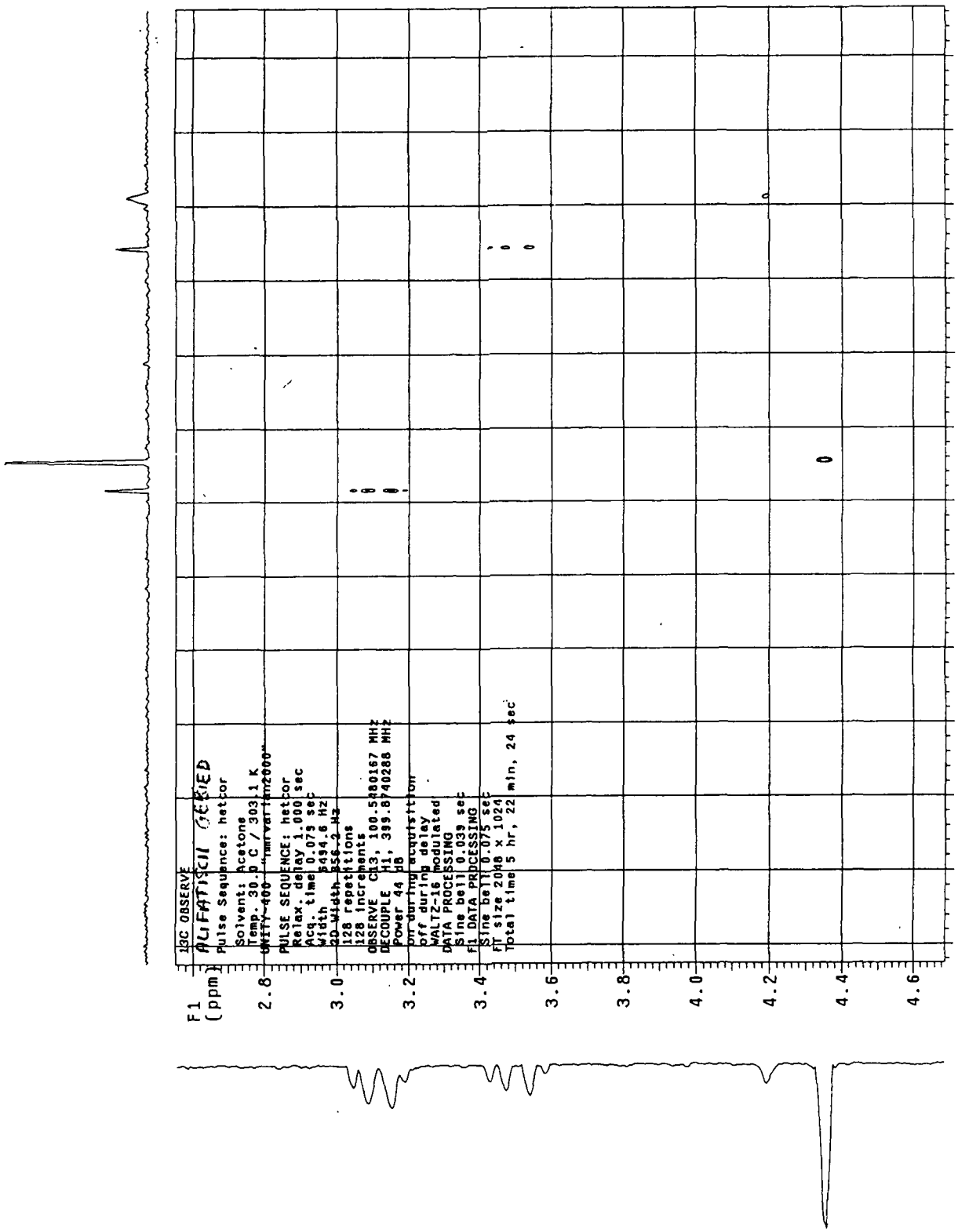
13C OBSERVE
ALIFATISCH GEKIED
Pulse Sequence: hetcor
Solvent: Acetone
Temp. 30.0 C / 303.1 K
UNITY-400 "unvartim2000"
PULSE SEQUENCE: hetcor
Relax. delay 1.000 sec
Acq. time 0.075 sec
Width 5494.6 Hz
2D Width 556.2 Hz
128 repetitions
128 increments
OBSERVE CL3, 100.5480167 MHz
DECOUPLE H1, 399.8740288 MHz
Power 44 dB
pr during acquisition
off during delay
WALTZ-16 modulated
DATA PROCESSING
Sine bell 0.039 sec
F1 DATA PROCESSING
Sine bell 0.075 sec
FT size 2048 x 1024
Total time 5 hr, 22 min, 24 sec
F1 (ppm)
F2 (ppm)

FIG. 8a

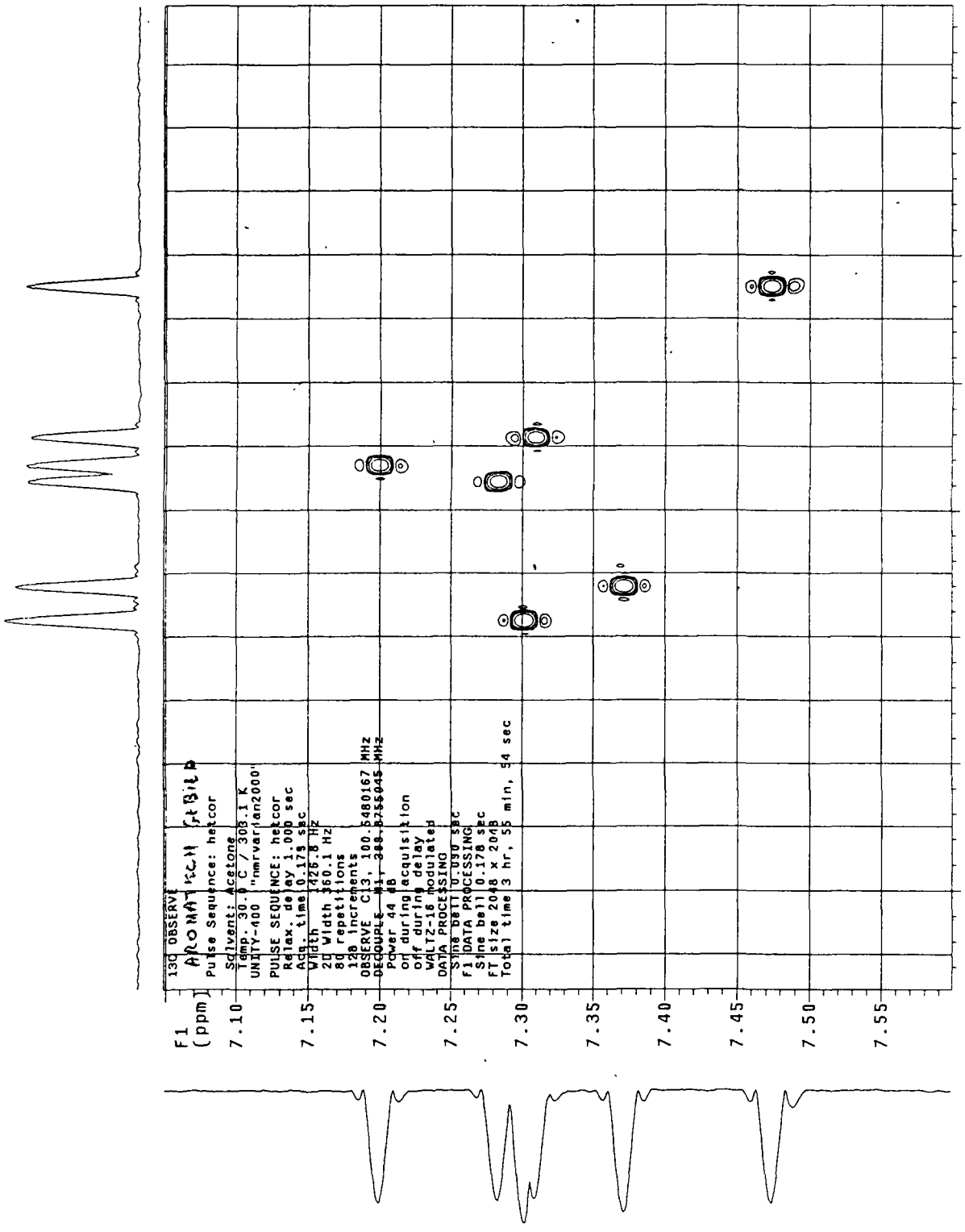
F1 (ppm)
7.10
7.15
7.20
7.25
7.30
7.35
7.40
7.45
7.50
7.55
F2 (ppm)
132
131
130
129
128
127
126
AROMATICS
Pulse Sequence: hetcor
Solvent: Acetone
Temp. 30.0 C / 303.1 K
UNITY-400 "nmrvar1an2000"
PULSE SEQUENCE: hetcor
Relax. delay 1.000 sec
Acq. time 0.179 sec
F1 Width 360.1 Hz
F2 Width 1426.8 Hz
80 repetitions
128 increments
OBSERVE C13, 100.5480167 MHz
DECOUPLE H1, 399.8755045 MHz
Power 44 dB
on during acquisition
off during delay
WALTZ-16 modulated
DATA PROCESSING
Sine bell 0.178 sec
F1 DATA PROCESSING
Sine bell 0.178 sec
FT size 2048 x 2048
Total time 3 hr, 55 min, 54 sec

FIG. 8b

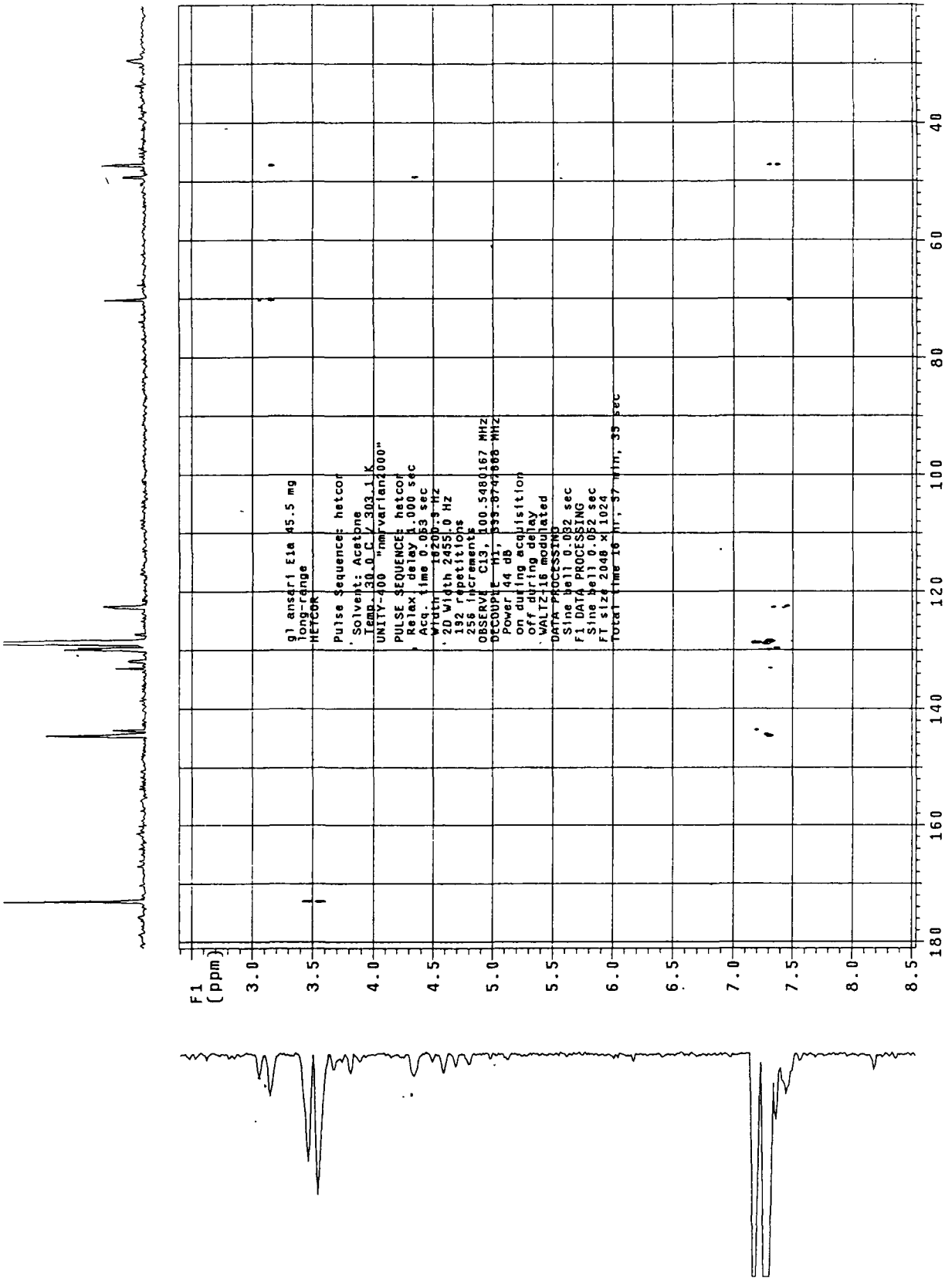
gl ansari Eia 45.5 mg
long-range
HETCOR
Pulse Sequence: hetcor
Solvent: Acetone
Temp. 30.0 C / 303.1 K
UNITY-400 "marvarian2000"
PULSE SEQUENCE: hetcor
Relax. delay 1.000 sec
Acq. time 0.053 sec
Width 10200.9 Hz
2D Width 2455.0 Hz
192 repetitions
256 increments
OBSERVE C13, 100.5480167 MHz
DECOUPLE H1, 399.8744800 MHz
Power 44 dB
on during acquisition
off during delay
WALTZ-16 modulated
DATA PROCESSING
Sine bell 0.032 sec
F1 DATA PROCESSING
Sine bell 0.052 sec
FT size 2048 x 1024
Total time 16 hr, 37 min, 33 sec
F1 (ppm)
F2 (ppm)

FIG. 9a

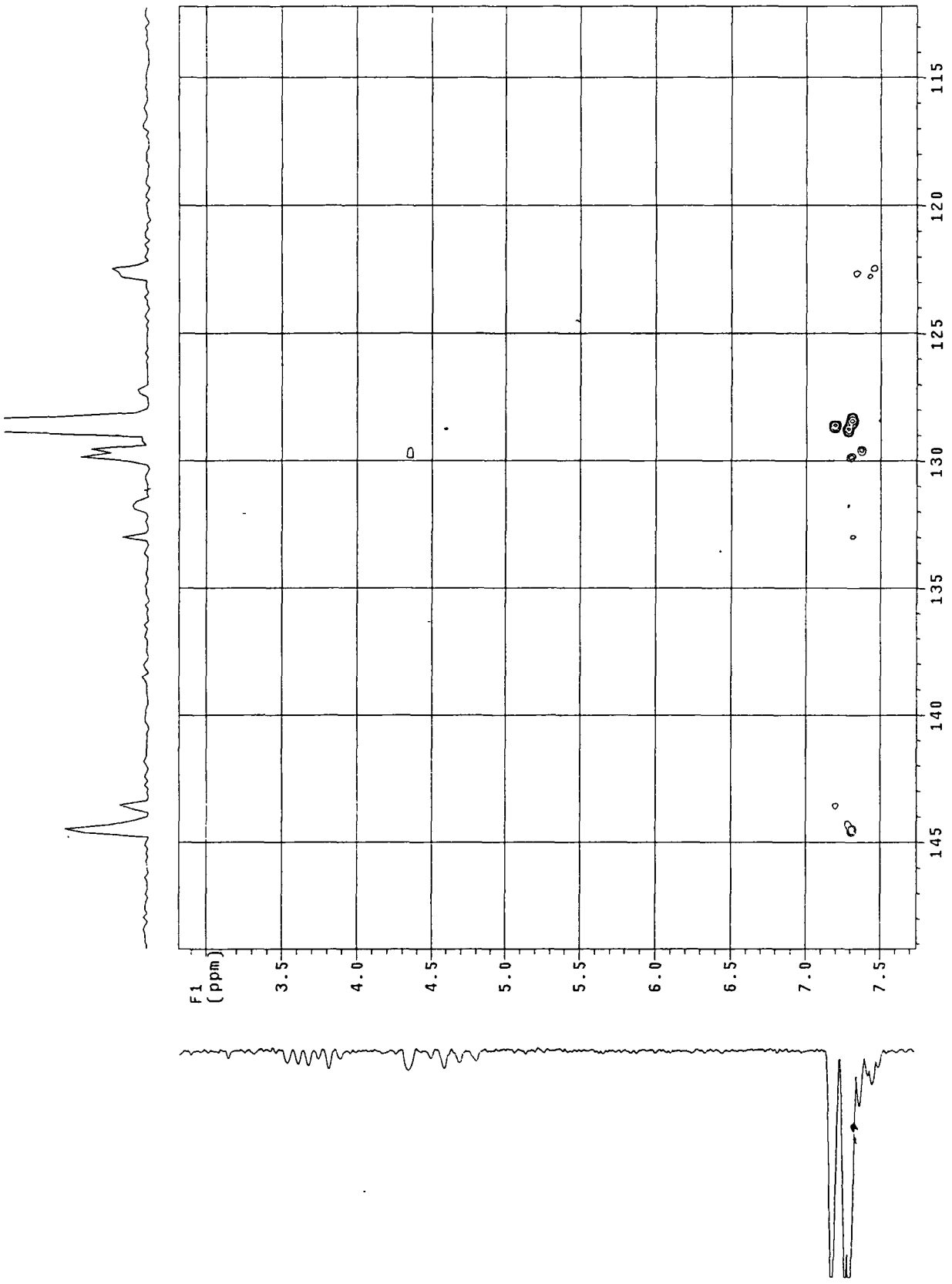

FIG. 9b

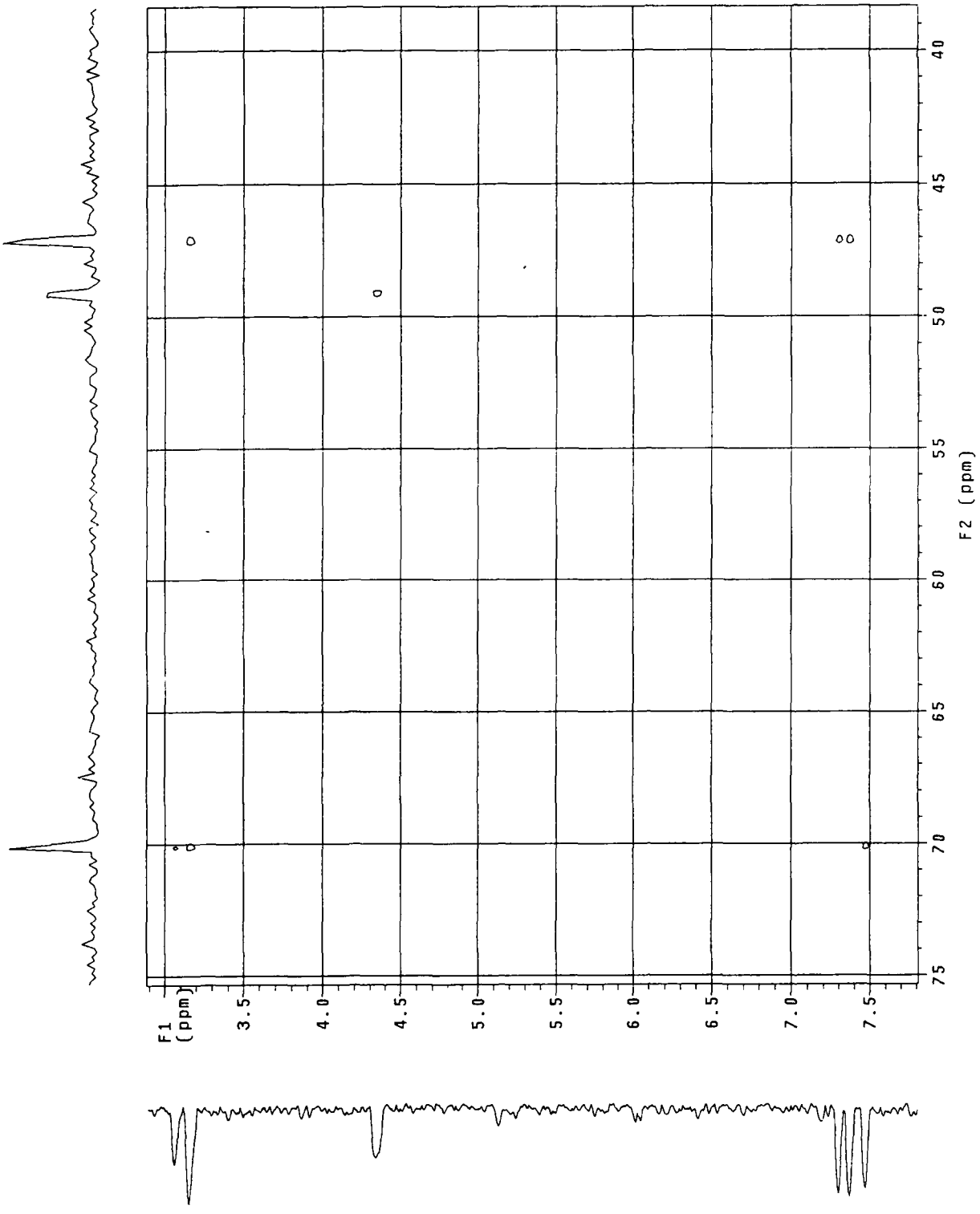

FIG. 9c

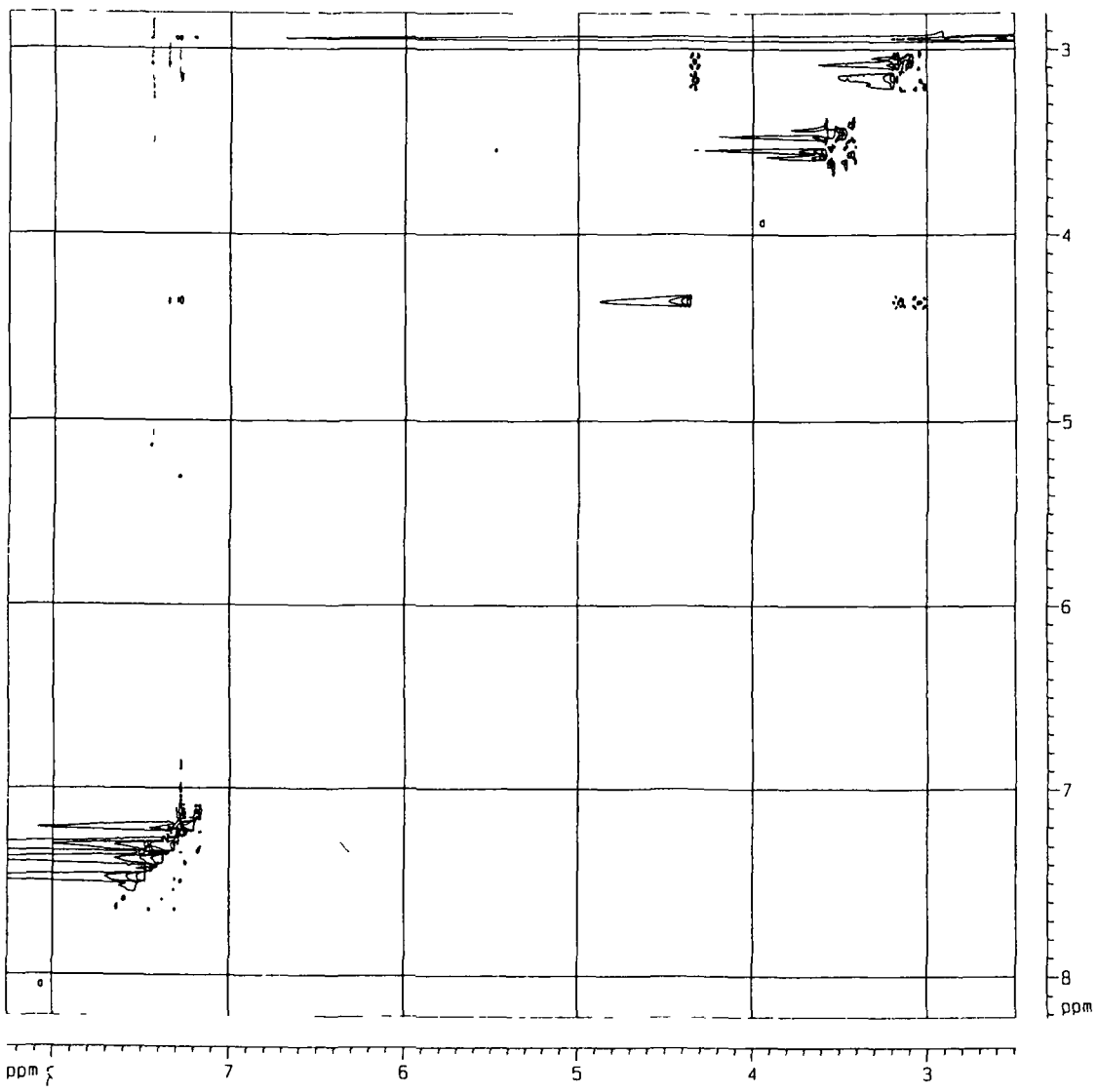

FIG. 10a

```
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NAME                    tim
EXPNO                     2
PROCNO                    1

            F2 - Acquisition Parameters
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Time                  20 05
INSTRUM               spect
PROBHD      5 mm Multinu
PULPROG             noesytp
TD                      1024
SOLVENT              Aceton
NS                        32
DS                        16
SWH                2394 636 Hz
FIDRES             2 338512 Hz
AQ                 0 2138612 sec
RG                     812 7
DW                   208 800 usec
DE                     4 50 usec
TE                   300 0 K
D0                 0 00000300 sec
D1                 2 00000000 sec
DB                 0 30000001 sec
IN0                0 00020880 sec

========== CHANNEL f1 ==========
NUC1                      1H
P1                     6 50 usec
PL1                   2 00 dB
SFO1              400 1322007 MHz

            F1 - Acquisition parameters
NDO                       2
TD                      512
SFO1               400 1322 MHz
FIDRES             4 677023 Hz
SW                   5 985 ppm

            F2   Processing parameters
SI                      2048
SF               400 1300104 MHz
WDW                     SINE
SSB                       2
LB                   0 00 Hz
GB                        0
PC                   1 00

            F1 - Processing parameters
SI                      1024
MC2                     TPPI
SF               400 1300037 MHz
WDW                     SINE
SSB                       2
LB                   0 00 Hz
GB                        0

            2D NMR plot parameters
CX2                  16 00 cm
CX1                  16 00 cm
F2PLO                8 259 ppm
F2LO               3304 62 Hz
F2PHI                2 490 ppm
F2HI                996 51 Hz
F1PLO                8 220 ppm
F1LO               3289 14 Hz
F1PHI                2 802 ppm
F1HI               1121 34 Hz
F2PPMCM              0 36053 ppm/cm
F2HZCM             144 25693 Hz/cm
F1PPMCM              0 33861 ppm/cm
F1HZCM             135 48752 Hz/cm
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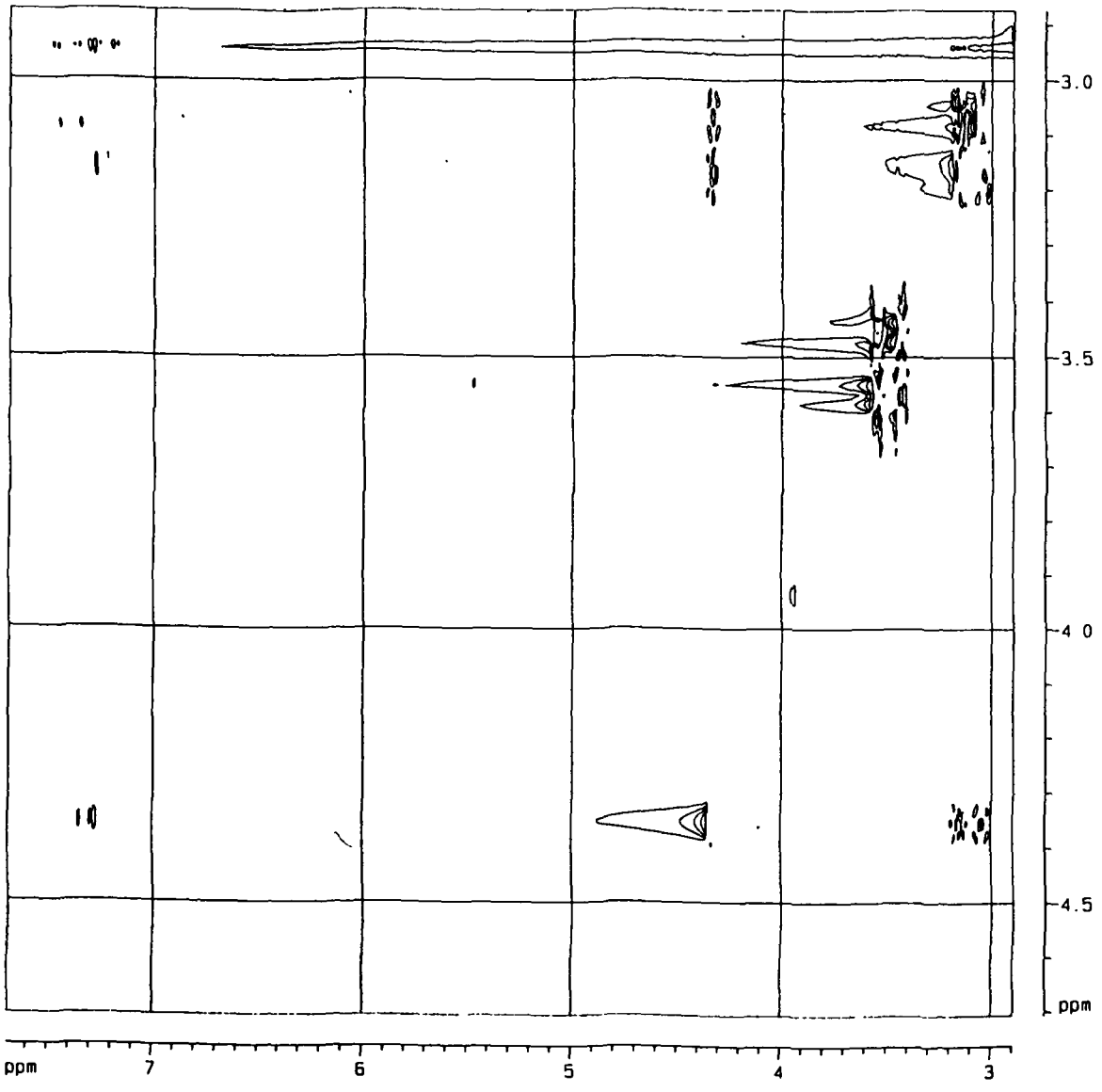


FIG. 10b

Current Data Parameters

NAME	tim
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20010226
Time	20 05
INSTRUM	spect
PROBHD	5 mm Multinu
PULPROG	noesytp
TD	1024
SOLVENT	Aceton
NS	32
DS	16
SWH	2394 636 Hz
FIDRES	2 338512 Hz
AQ	0 2138612 sec
RG	812 7
DW	208 800 usec
DE	4 50 usec
TE	300 0 K
D0	0 00000300 sec
D1	2 00000000 sec
D8	0 30000001 sec
IN0	0 00020880 sec

********** CHANNEL f1 **********

NUC1	1H
P1	6 50 usec
PL1	-2 00 dB
SFO1	400 1322007 MHz

F1 - Acquisition parameters

NDO	2
TD	512
SFO1	400 1322 MHz
FIDRES	4 677023 Hz
SW	5 985 ppm

F2 - Processing parameters

SI	2048
SF	400 1300104 MHz
WDW	SINE
SSB	2
LB	0 00 Hz
GB	0
PC	1 00

F1 - Processing parameters

SI	1024
MC2	TPPI
SF	400 1300037 MHz
WDW	SINE
SSB	2
LB	0 00 Hz
GB	0

2D NMR plot parameters

CX2	16 00 cm
CX1	16 00 cm
F2PLO	7 689 ppm
F2LO	3076 61 Hz
F2PHI	2 897 ppm
F2HI	1159 03 Hz
F1PLO	4 708 ppm
F1LO	1883.70 Hz
F1PHI	2 873 ppm
F1HI	1149 40 Hz
F2PPMCM	0 29952 ppm/cm
F2HZCM	119 84872 Hz/cm
F1PPMCM	0 11470 ppm/cm
F1HZCM	45 88329 Hz/cm

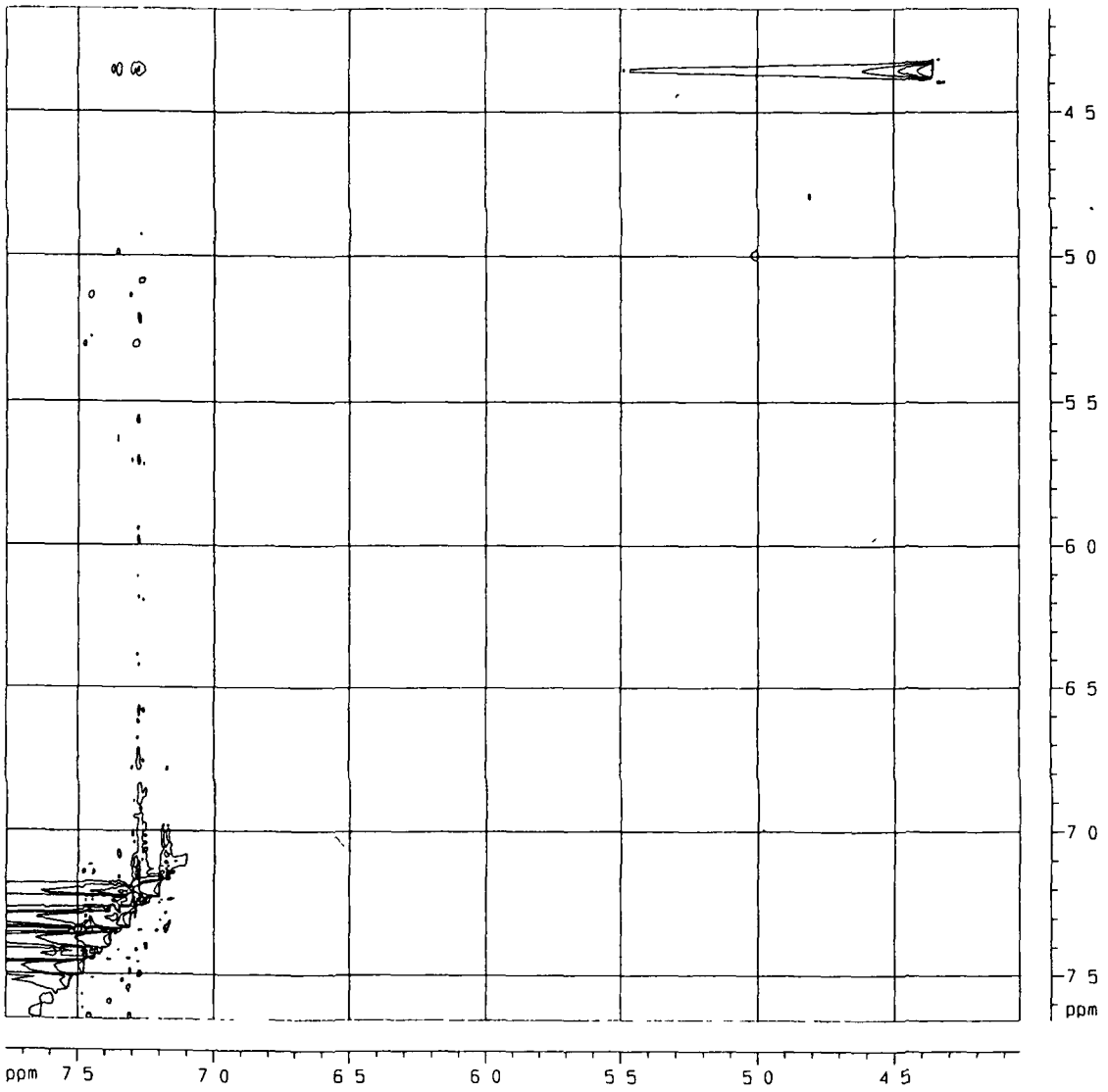


FIG. 10c

```
                Current Data Parameters
NAME                    tim
EXPNO                     2
PROCNO                    1

          F2 - Acquisition Parameters
Date_              20010226
Time                 20 05
INSTRUM              spect
PROBHD     5 mm Multinu
PULPROG           noesytp
TD                   1024
SOLVENT             Aceton
NS                     32
DS                     16
SWH              2394 636 Hz
FIDRES           2 338512 Hz
AQ               0 2138612 sec
RG                   812 7
DW                208 800 usec
DE                  4 50 usec
TE                  300 0 K
D0               0 00000300 sec
D1               2 00000000 sec
DB               0 30000001 sec
IN0              0 00020880 sec

========== CHANNEL f1 ==========
NUC1                   1H
P1                  6 50 usec
PL1                -2 00 dB
SFO1           400 1322007 MHz

          F1 - Acquisition parameters
ND0                       2
TD                      512
SFO1             400 1322 MHz
FIDRES           4 677023 Hz
SW                 5 985 ppm

          F2 - Processing parameters
SI                     2048
SF            400 1300104 MHz
WDW                    SINE
SSB                       2
LB                 0 00 Hz
GB                        0
PC                 1 00

          F1 - Processing parameters
SI                     1024
MC2                    TPPI
SF            400 1300037 MHz
WDW                    SINE
SSB                       2
LB                 0 00 Hz
GB                        0

        2D NMR plot parameters
CX2                16 00 cm
CX1                16 00 cm
F2PLO               7 765 ppm
F2LO              3107 01 Hz
F2PHI               4 042 ppm
F2HI              1617 38 Hz
F1PLO               7 659 ppm
F1LO              3064 64 Hz
F1PHI               4 135 ppm
F1HI              1654 52 Hz
F2PPMCM          0 23268 ppm/cm
F2HZCM          93 10200 Hz/cm
F1PPMCM          0 22026 ppm/cm
F1HZCM          88 13267 Hz/cm
```

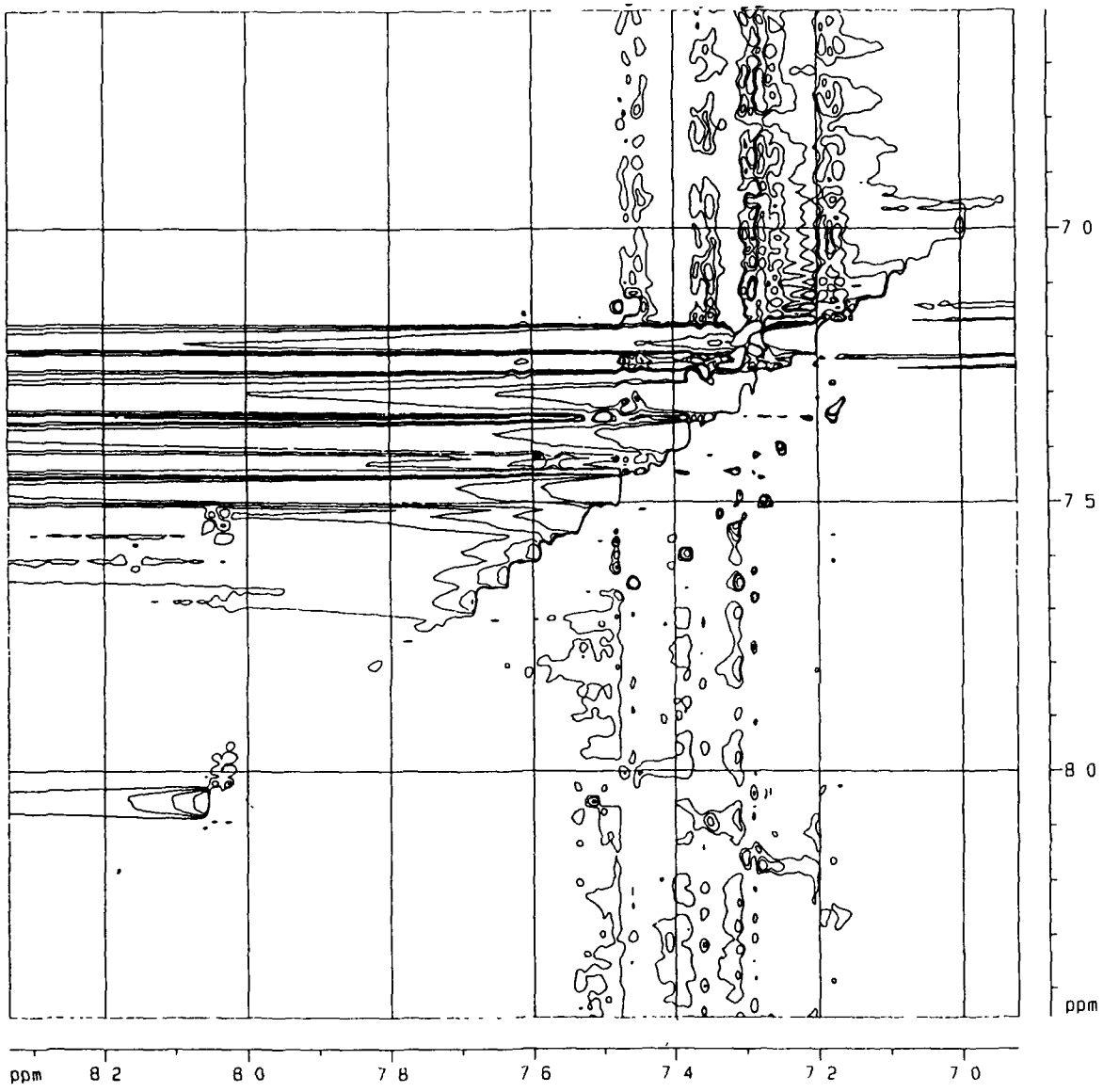


FIG. 10d

Current Data Parameters

NAME	tim
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20010226
Time	20 05
INSTRUM	spect
PROBHD	5 mm Multinu
PULPROG	noesytp
TD	1024
SOLVENT	Aceton
NS	32
DS	16
SWH	2394 636 Hz
FIDRES	2 338512 Hz
AQ	0 2138612 sec
RG	812 7
DW	208 800 usec
DE	4 50 usec
TE	300 0 K
D0	0 00000300 sec
D1	2 00000000 sec
D8	0 30000001 sec
IN0	0 00020880 sec

********** CHANNEL f1 **********

NUC1	1H
P1	6 50 usec
PL1	-2 00 dB
SFO1	400 1322007 MHz

F1 - Acquisition parameters

NDO	2
TD	512
SFO1	400 1322 MHz
FIDRES	4 677023 Hz
SW	5 985 ppm

F2 - Processing parameters

SI	2048
SF	400 1300104 MHz
WDW	SINE
SSB	2
LB	0 00 Hz
GB	0
PC	1 00

F1 - Processing parameters

SI	1024
MC2	TPPI
SF	400 1300037 MHz
WDW	SINE
SSB	2
LB	0 00 Hz
GB	0

2D NMR plot parameters

CX2	16 00 cm
CX1	16 00 cm
F2PLO	8 335 ppm
F2LO	3335 02 Hz
F2PHI	6 923 ppm
F2HI	2770 27 Hz
F1PLO	8 454 ppm
F1LO	3382 68 Hz
F1PHI	6 601 ppm
F1HI	2641 37 Hz
F2PPMCM	0 08821 ppm/cm
F2HZCM	35 29691 Hz/cm
F1PPMCM	0 11579 ppm/cm

according to Karplus[121], the coupling constants $J_{1'up,2'}$ and $J_{1'dn,2'}$ indicated an antiperiplanar torsion angle for H_{dn}-1' and H-2', and a synclinal torsion angle for H_{up}-1' and H-2' i.e. the coupling constant, revealed a synclinal position of H-2' relative to the diastereotopic hydrogen atoms H-1'up and H-1'dn. This was further confirmed by a NOE-correlation of H-2' with both H-1'up and H-1'dn (**TABLES 2** and **3**). Thus, the most preferred conformation of (**3**) deduced on the basis of above spectral techniques, is presented in **FIG. 1.**

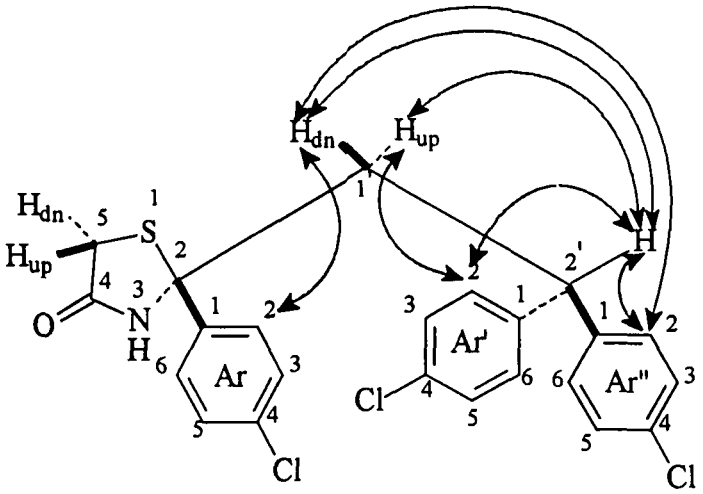
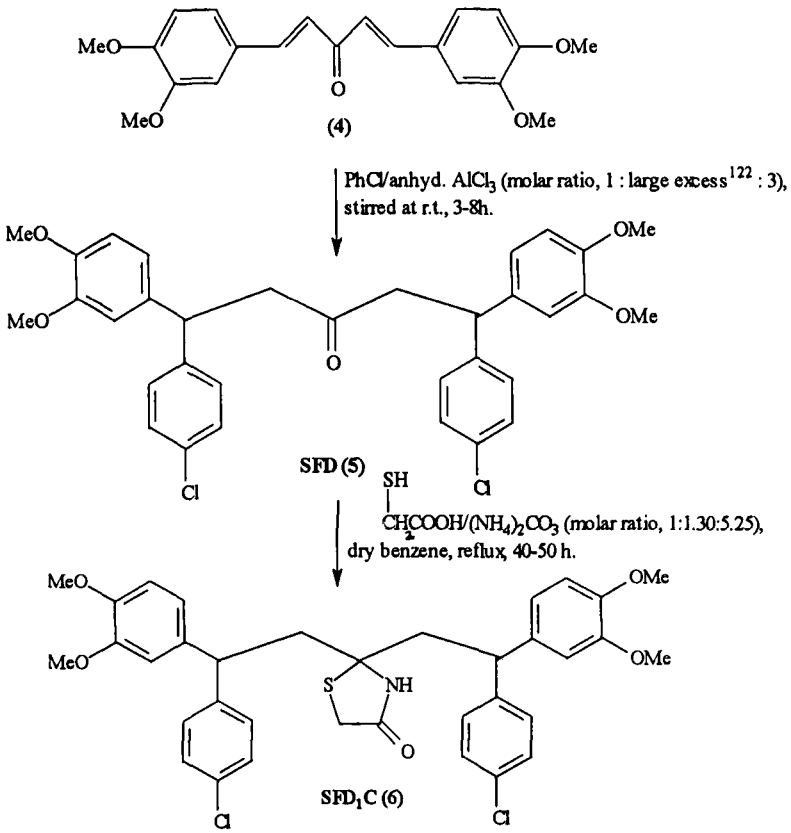


FIG. - 1

Synthesis of 2,2-di[2-(4-chlorophenyl)-2-(3,4-dimethoxyphenyl) ethyl]thiazolidin-4-one SFD_{1C} (6) from 1,5-bis(3,4-dimethoxyphenyl) pent-1,4-dien-3-one(4) via 1,5-bis(4-chlorophenyl)-1,5-bis(3,4-dimethoxyphenyl)pentan-3-one SFD (5) using thioglycollic acid in the presence of ammonium carbonate.

The compound SFD_{1C} (6) was prepared as mentioned above. The adduct **SFD (5)** was first prepared by treating the dienone **(4)** (prepared according to published procedure)[122] with excess of chlorobenzene and anhydrous aluminium chloride as yellow semi-solid mass in 70% yield. It was then reacted with thioglycollic acid and ammonium carbonate (molar ratio, 1:1.30:5.25) in refluxing benzene for 40 h. The products on purification by column chromatography (silica gel, pet. ether-diethyl ether, 7:3 v/v) followed by crystallization (benzene-acetone, 9:1 v/v) afforded SFD_{1C} (6) as white crystalline globules in 55% yield.

The outline of synthesis is presented below.



Structure Elucidation of SFD (5)

It is a yellow semi solid mass and appears brown on exposure to iodine vapours (TLC). The constitution of **SFD** has been established by FT-IR, FAB-MS, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum (KBr) displayed characteristic absorption bands at 2928 (CH), 1711 (C=O), 1595, 1476 (phenyl), 1356, 1090, 1016, 759, 603 cm^{-1}. In FAB-MS spectrum of **SFD** (**FIG. 11**) the molecular ion peak $[M]^{+}$ was absent but sets of peaks at m/z 541/543, 529/531, 491/493/495, 235/237, 165/167, 149/151, 125/127 etc. arised mostly by demethoxylation/dechlorination confirmed that its molecular weight was 578/580/582 (**CHART-3**). The ^{1}H- and ^{13}C-NMR spectra of **SFD** dissolved in $CDCl_3$ showed signals as assigned in **TABLE 4**. The assignments of all ^{1}H- and ^{13}C-NMR signals to individual H- and C-atoms have been performed on the basis of typical chemical shift values, multiplicity, relative integrations and also by comparison with the spectral data of **P(2) (TABLE-1)**. The ^{1}H-NMR spectrum (**FIG. 12**) showed a double doublet at δ4.43 (J=13.20Hz and 6.60Hz) and an another double doublet at δ4.47 (J=13.20Hz and 6.30Hz) which were attributed to $H_{2up/4up}$ and $H_{2dn/4dn}$. A double doublet at δ4.99 (J=6.60Hz and 6.30Hz) was assigned to H-1/5. Thus, the coupling constants suggested that the two diastereotopic hydrogens at C-2/C-4 are antiperiplanar and synperiplanar with the hydrogen at C-1/C-5. The singlet at δ3.13 was accounted for four methoxy groups. The aromatic protons signals for four benzene rings consiting of fourteen protons were also attributed as shown in **TABLE-4**. The ^{13}C-NMR spectrum (**FIG. 13**) showed a signal at δ205.1 for carbonyl carbon and the signals at δ41.30 and δ48.90 were assigned to C-2/4 and C-1/5.The signal at δ44.5 was attributed to methoxycarbons. The aromatic carbons signals were assigned as shown in the **TABLE-4**.

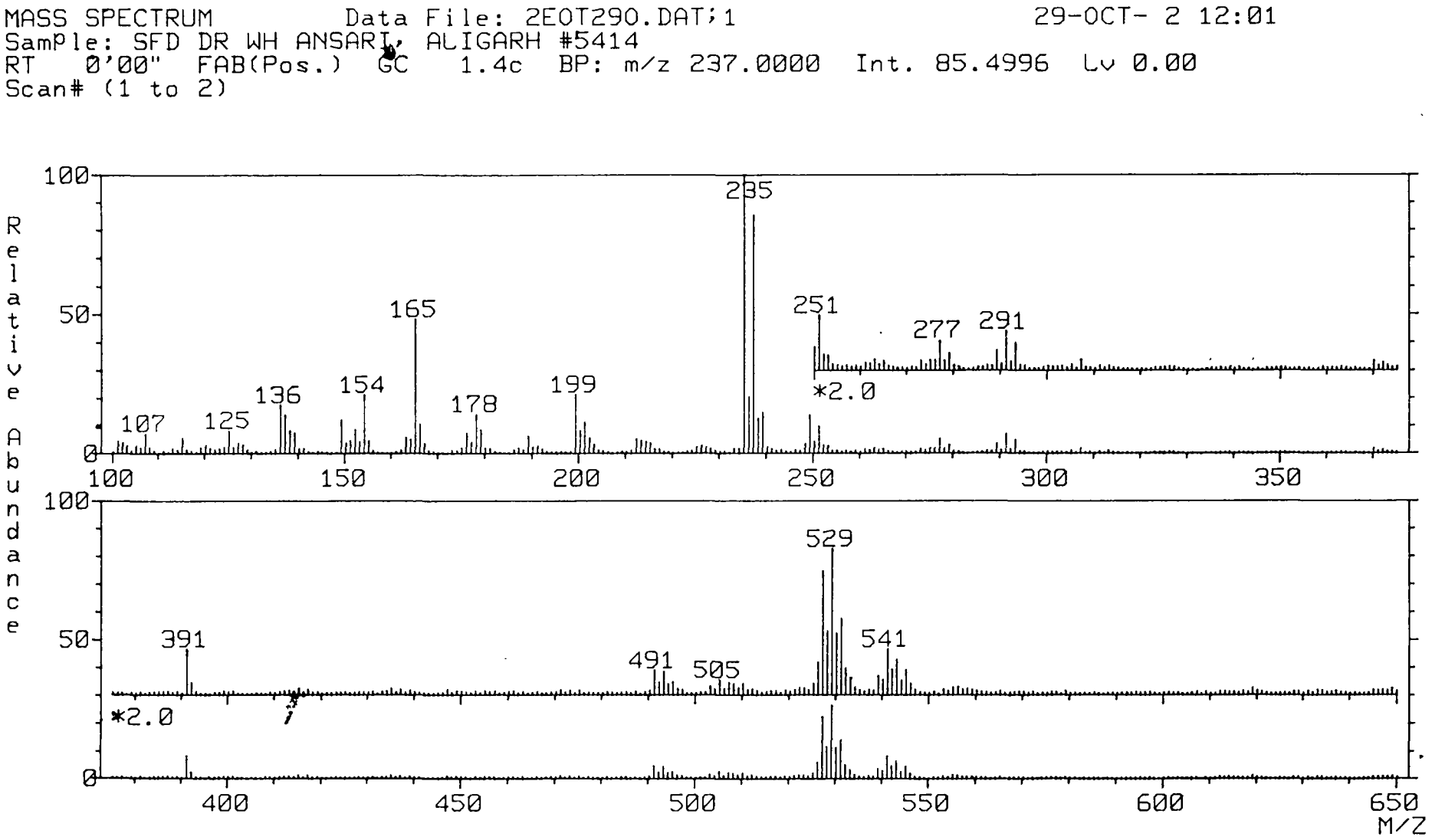

MASS SPECTRUM Data File: 2EOT290.DAT;1 29-OCT- 2 12:01
Sample: SFD DR WH ANSARI, ALIGARH #5414
RT 0'00" FAB(Pos.) GC 1.4c BP: m/z 237.0000 Int. 85.4996 Lv 0.00
Scan# (1 to 2)
Relative Abundance
100
50
0
235
165
251
277
291
136
154
178
199
107
125
*2.0
100
150
200
250
300
350
529
391
491
505
541
*2.0
400
450
500
550
600
650
M/Z

FIG. 11

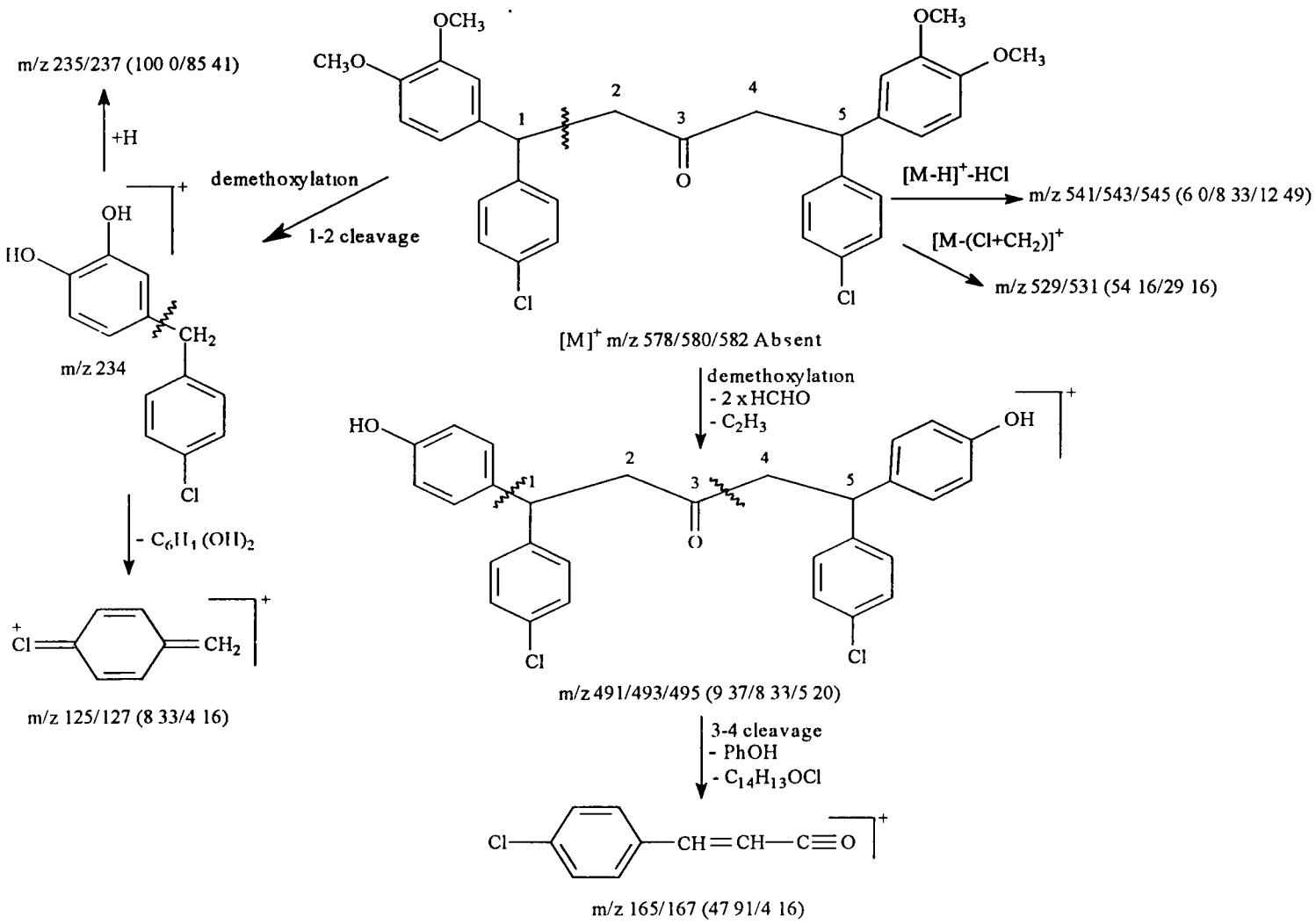

m/z 235/237 (100 0/85 41)
+H
demethoxylation
1-2 cleavage
[M-H]+-HCl
m/z 541/543/545 (6 0/8 33/12 49)
[M-(Cl+CH2)]+
m/z 529/531 (54 16/29 16)
[M]+ m/z 578/580/582 Absent
m/z 234
- C6H1 (OH)2
m/z 125/127 (8 33/4 16)
demethoxylation
- 2 x HCHO
- C2H3
m/z 491/493/495 (9 37/8 33/5 20)
3-4 cleavage
- PhOH
- C14H13OCl
m/z 165/167 (47 91/4 16)

CHART - 3

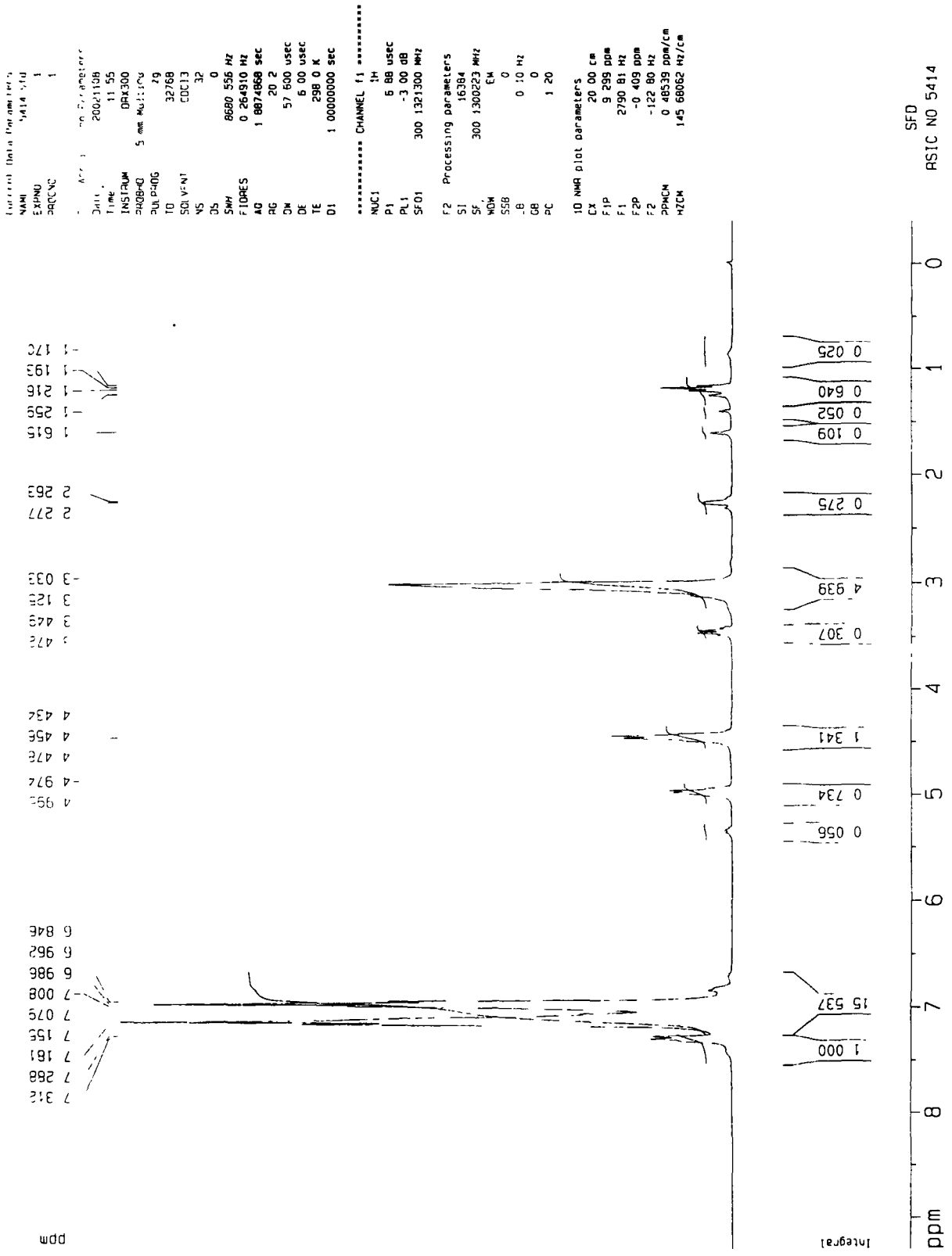

SFD
RSIC NO 5414
ppm
Integral
1 000
15 537
0 734
0 307
4 939
0 275
0 109
0 052
0 640
0 025

FIG. 12

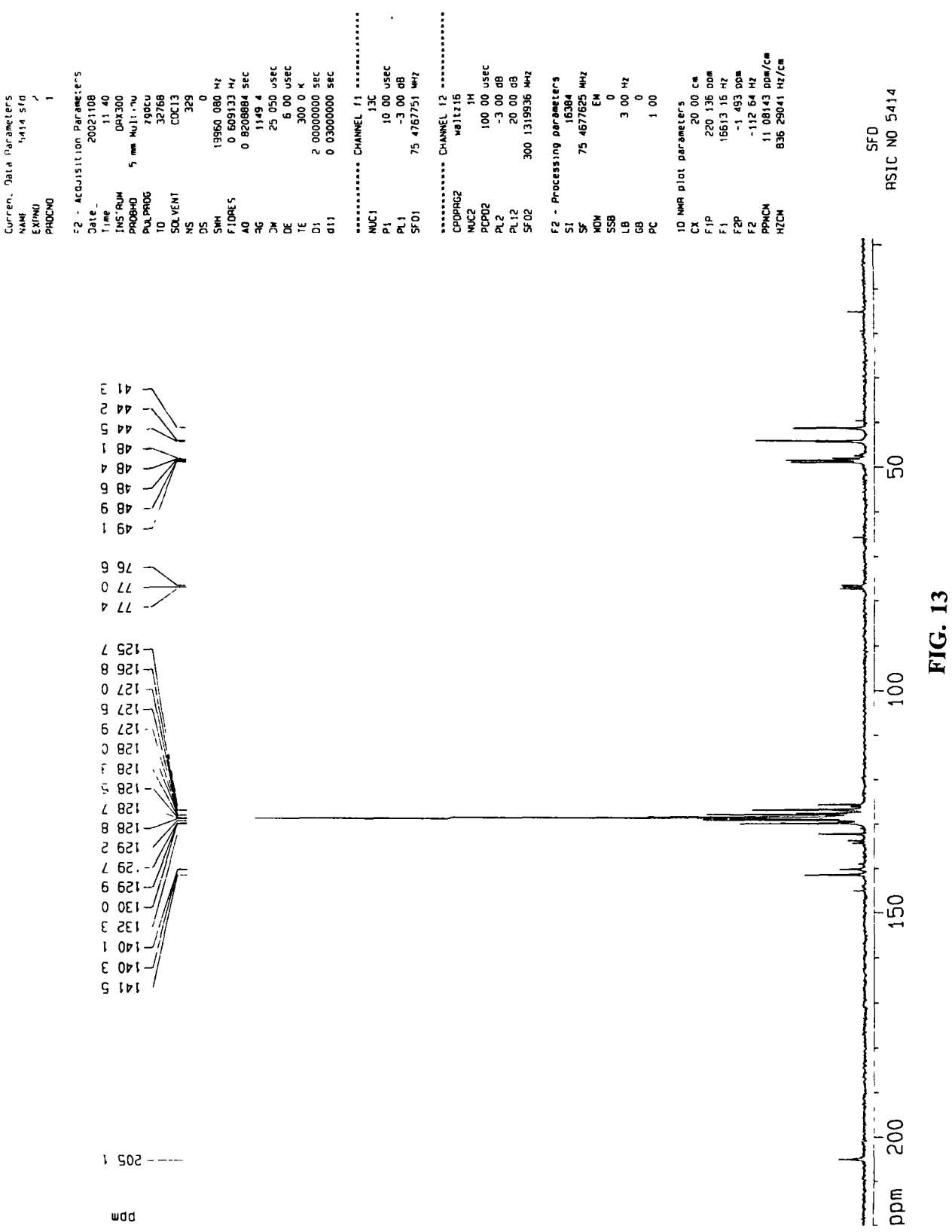
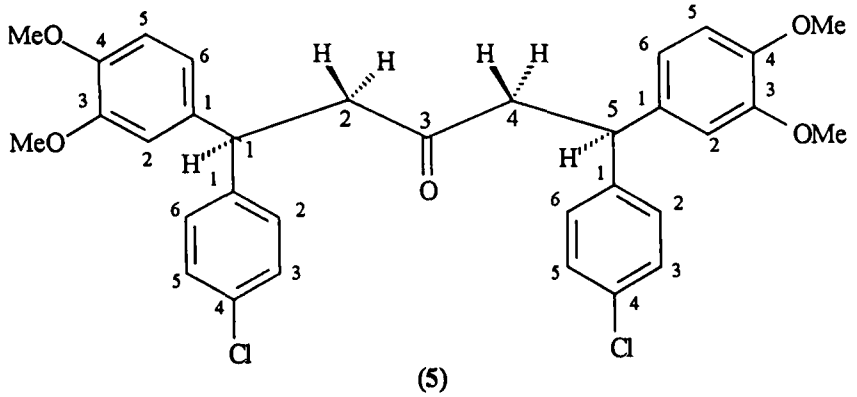

Curren. Data Parameters
NAME 5414 sfd
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20021108
Time 11 40
INSTRUM DRX300
PROBHD 5 mm Multinu
PULPROG zgdcu
TD 32768
SOLVENT CDCl3
NS 329
DS 0
SWH 13960.080 Hz
FIDRES 0.609133 Hz
AQ 0.8208884 sec
RG 1149.4
DW 25.050 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
CHANNEL f1
NUC1 13C
P1 10.00 usec
PL1 -3.00 dB
SFO1 75.4767751 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -3.00 dB
PL12 20.00 dB
SFO2 300.1319936 MHz
F2 - Processing parameters
SI 16384
SF 75.4677625 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 220.136 ppm
F1 16613.16 Hz
F2P -1.493 ppm
F2 -112.64 Hz
PPMCM 11.08143 ppm/cm
HZCM 836.29041 Hz/cm
SFD
ASIC NO 5414
ppm
200
150
100
50

FIG. 13

TABLE -4 : ^{1}H-NMR and ^{13}C-NMR spectral data of SFD (5)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)	C-nr	δ(ppm)
2up/4up	4.43	2H	dd	$J_{2up/4up,2dn/4dn}$= 13.20	2/4	41.30
				$J_{2up/4up,1/5}$ = 6.60		
2dn/4dn	4.47	2H	dd	$J_{2up/4up,2dn/4dn}$= 13.20	1/5	48.90
				$J_{2dn/4dn,1/5}$= 6.30		
1/5	4.99	1H	dd	$J_{2up/4up,1/5}$=6.60	4 x OCH_3	44.50
				$J_{2dn/4dn,1/5}$=6.30	3	205.1
4 x OCH_3	3.13	12H	s		4 x Ar	125.70-141.45
4 x Ar	6.84-7.31	14H	br m			

On the basis of these facts, **SFD** was characterised as *1,5-bis (4-chlorophenyl)-1,5-bis(3,4-dimethoxyphenyl)pentan-3-one* ***(5)***.



(5)

Structure Elucidation of SFD_{1C} (6)

It is a white globules shaped crystalline solid, m.p 204 °C and appears light brown on exposure to iodine vapours (TLC). The constitution of $\mathbf{SFD_{1C}}$ has been fully established by FT-IR, EI-MS, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum (KBr) showed characteristic absorption bands at 3400 (NH), 2912 (CH), 1674 (-CONH), 1594 (Phenyl), 1485 (S-CH_2), 1410 (C–N), 1366, 1239, 1208, 1092, 1012, 818, 780 cm^{-1}. The EI-MS spectrum (**FIG. 14**) of $\mathbf{SFD_{1C}}$ showed no molecular ion peak but the peaks observed at m/z 528, 352, 236, 203, 165 obtained by fragmentations of $[M+1]^+$ as shown in **CHART-4**, confirmed its molecular weight to be 651. This is equal to the sum of the molecular weights of the adduct **(5)** (578), thioglycollic acid (92) and ammonia (17) minus two molecules of water (36). This indicated that the formation of thiazolidinone ring has occurred by the cyclocondensation of the adduct **SFD (5)** with thioglycollic acid and ammonia. The base peak at m/z 236/238 (100/12.88) corresponding with the fragment ion $[p\text{-}ClC_6H_4C_5H_3ONS]^+$ indicated the location of ring. The ^{1}H-NMR (**FIG. 15**) and ^{13}C-NMR (**FIG. 16**) spectra of $\mathbf{SFD_{1C}}$ dissolved in $CDCl_3$ showed signals

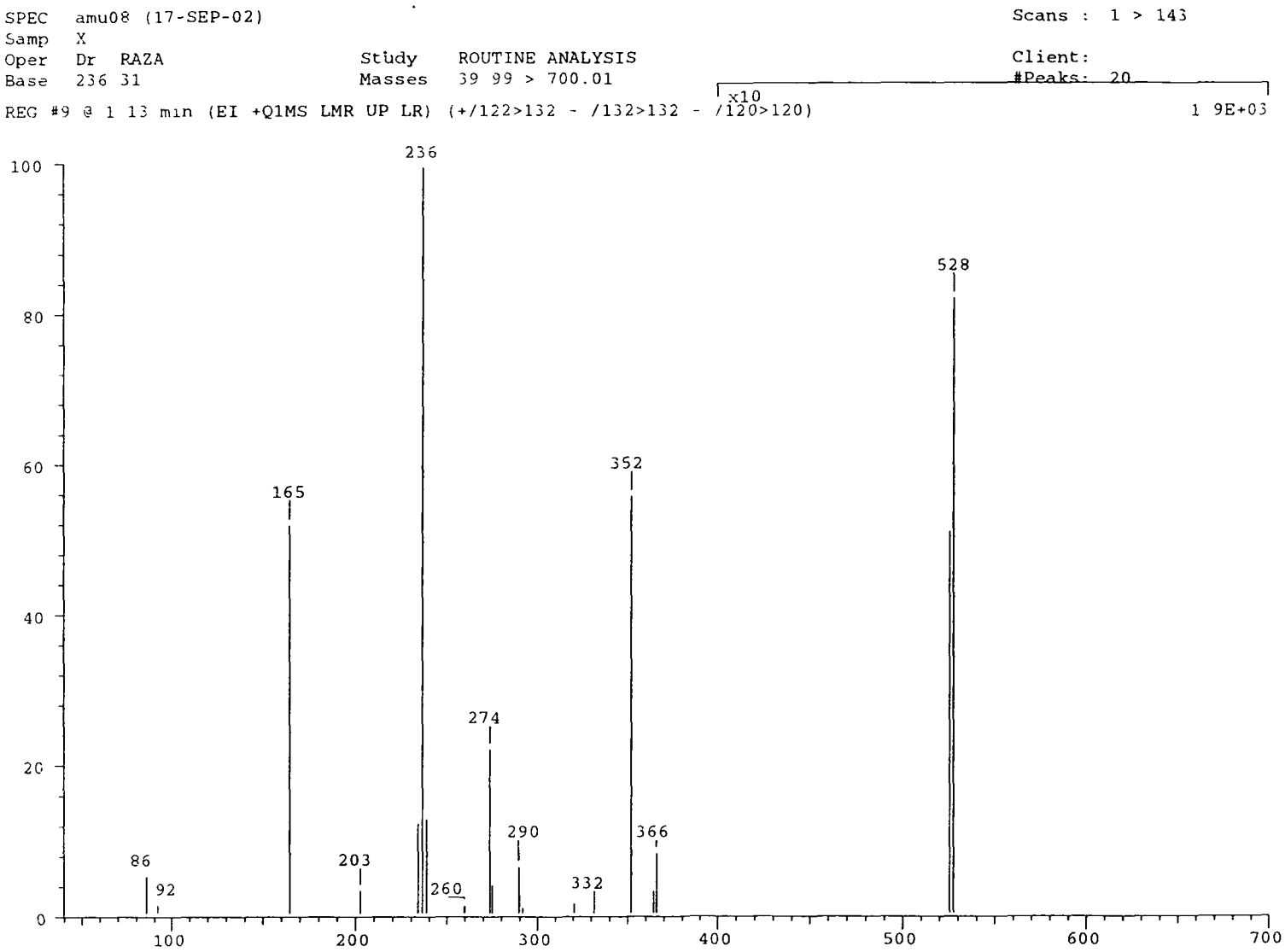

SPEC amu08 (17-SEP-02)
Samp X
Oper Dr RAZA
Base 236 31
Study ROUTINE ANALYSIS
Masses 39 99 > 700.01
Scans : 1 > 143
Client:
#Peaks: 20
REG #9 @ 1 13 min (EI +Q1MS LMR UP LR) (+/122>132 - /132>132 - /120>120)
x10
1 9E+03
100
80
60
40
20
0
100
200
300
400
500
600
700
236
528
352
165
274
290
366
86
92
203
260
332

FIG. 14

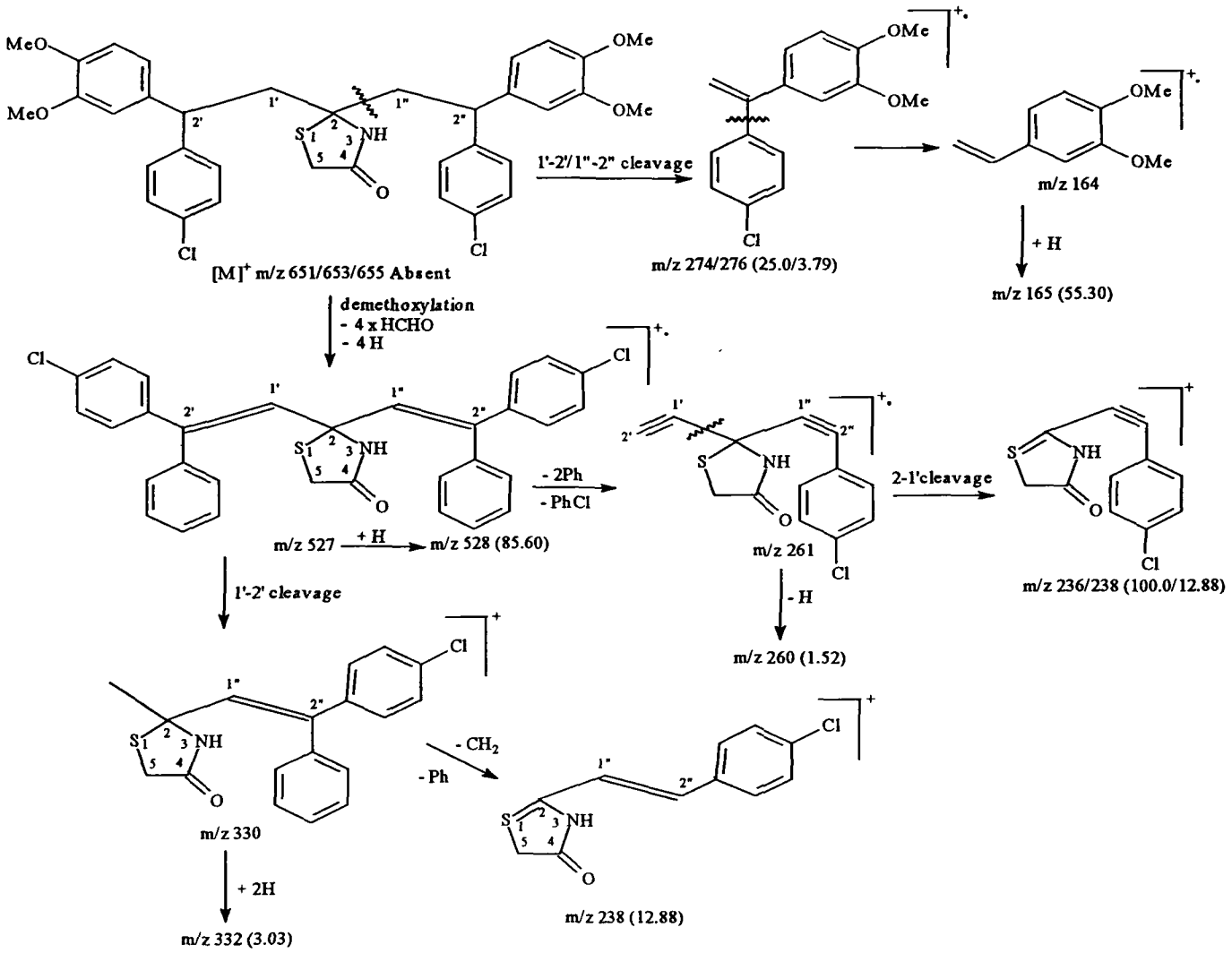

MeO
MeO
OMe
OMe
Cl
Cl
1'-2'/1"-2" cleavage
m/z 274/276 (25.0/3.79)
m/z 164
+ H
m/z 165 (55.30)
[M]+ m/z 651/653/655 Absent
demethoxylation
- 4 x HCHO
- 4 H
m/z 527
+ H
m/z 528 (85.60)
- 2Ph
- PhCl
m/z 261
2-1'cleavage
m/z 236/238 (100.0/12.88)
- H
m/z 260 (1.52)
1'-2' cleavage
m/z 330
+ 2H
m/z 332 (3.03)
- CH2
- Ph
m/z 238 (12.88)

CHART - 4

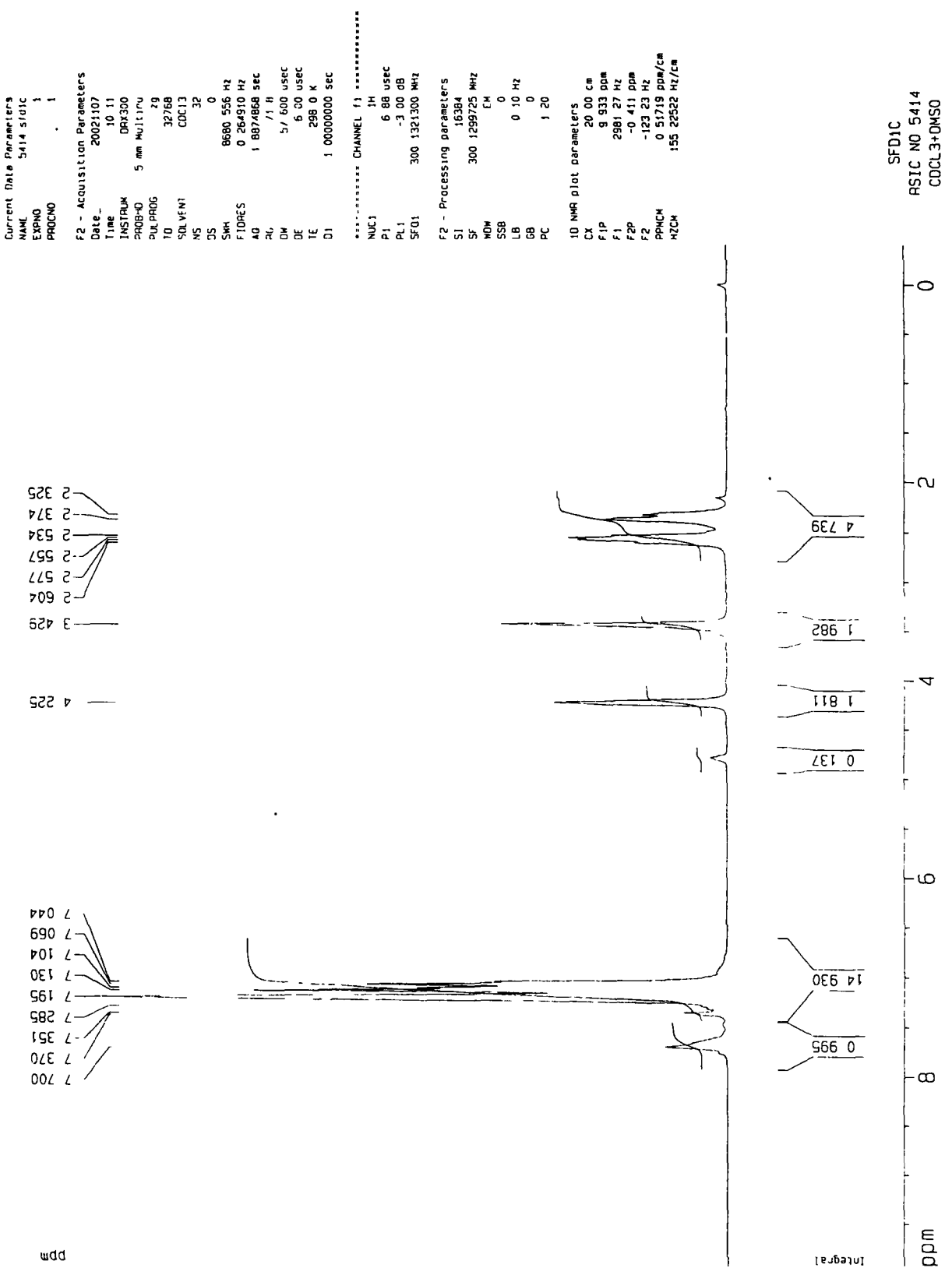

Current Data Parameters
NAME 5414 sfdic
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20021107
Time 10 11
INSTRUM DRX300
PROBHD 5 mm Multinu
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 32
DS 0
SWH 8680 556 Hz
FIDRES 0 264910 Hz
AQ 1 8874868 sec
RG /1 H
DW 57 600 usec
DE 6 00 usec
TE 298 0 K
D1 1 00000000 sec
CHANNEL f1
NUC1 1H
P1 6 88 usec
PL1 -3 00 dB
SFO1 300 1321300 MHz
F2 - Processing parameters
SI 16384
SF 300 1299725 MHz
WDW EM
SSB 0
LB 0 10 Hz
GB 0
PC 1 20
1D NMR plot parameters
CX 20 00 cm
F1P 9 933 ppm
F1 2981 27 Hz
F2P -0 411 ppm
F2 -123 23 Hz
PPMCM 0 51719 ppm/cm
HZCM 155 22522 Hz/cm
SFD1C
ASIC NO 5414
CDCL3+DMSO
7 700
7 370
7 351
7 285
7 195
7 130
7 104
7 069
7 044
4 225
3 429
2 604
2 577
2 557
2 534
2 374
2 325
14 930
0 995
4 739
1 982
1 811
0 137
ppm
Integral

FIG. 15

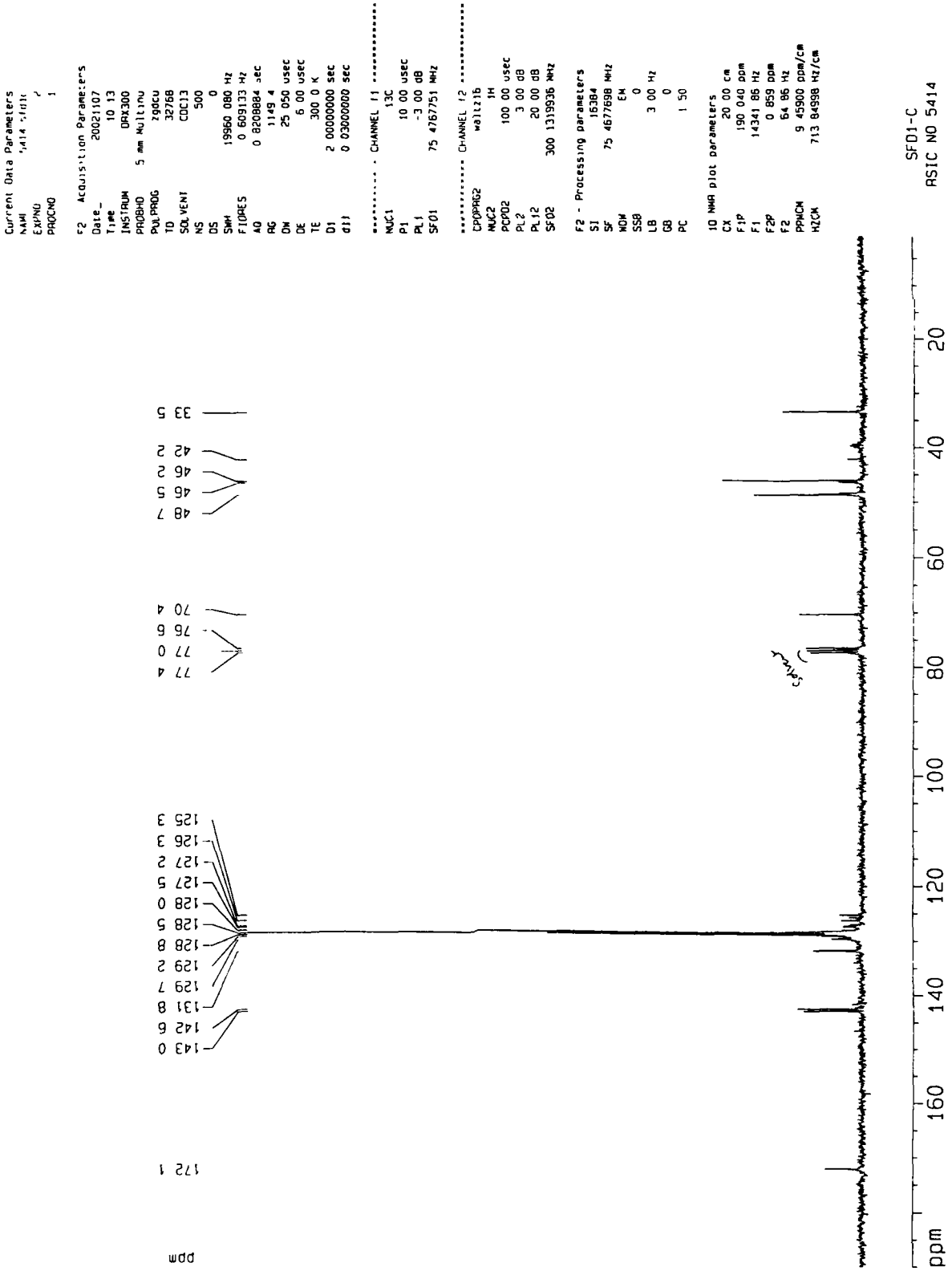

Current Data Parameters
F2 Acquisition Parameters
F2 - Processing parameters
1D NMR plot parameters
SFO1-C
RSIC NO 5414
ppm

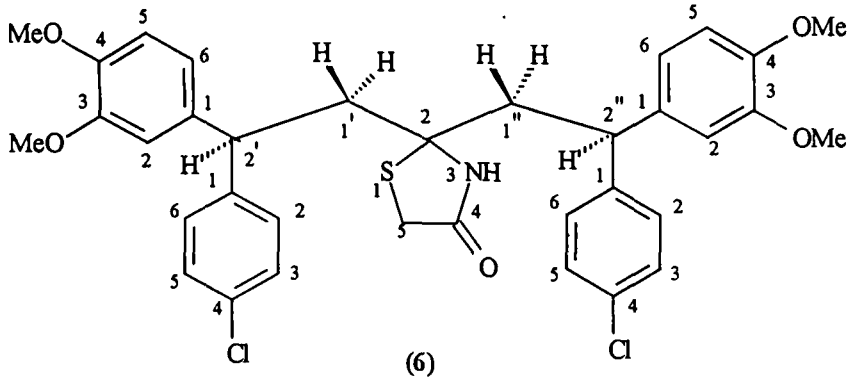
FIG. 16

TABLE - 5 : ^{1}H-NMR and ^{13}C-NMR spectral data of SFD_{1C} (6)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)	C-nr	δ(ppm)
1'up/1"up	2.35	2H	dd	$J_{1'up/1"up,1'dn/1"dn}$ = 14.70	1'/1"	48.70
				$J_{1'up/1"up,\ 2'/2"}$ = 4.80	2'/2"	42.20
1'dn/1"dn	2.58	2H	dd	$J_{1'up/1"up,1'dn/1"dn}$ = 14.70	2	70.40
				$J_{1'dn/1"dn,\ 2'/2"}$ = 6.90	4	172.10
2'/2"	4.70	1H	-	J = not resolved	5	33.50
H-5	4.22	2H	s	-		
4 x OCH_3	3.43	12H	s	-	4 x OCH_3	46.34
NH	7.70	1H	s	-		
4 x Ar	7.04-7.37	14H	br m	-	4 x Ar	125.30-143.0

as assigned (**TABLE-5**). The assignments of all ^{1}H-NMR and ^{13}C-NMR signals to specific H- and C-atoms have been performed on the basis of their typical chemical shift values, their coupling constants, relative integrations and by comparison with ^{1}H-NMR and ^{13}C-NMR spectral data of the adduct **SFD (5) (TABLE-4)** and the 4-thiazolidinone **E_{1A}(3) (TABLE-2** and **3)**. The ^{1}H-NMR spectrum of **SFD_{1C}** showed a singlet at δ7.70 for NH proton. The chemical shifts of C-2/C-4 protons of the adduct **SFD (5)** (**TABLE-4**) were shifted to higher fields from δ4.43-4.47 to δ2.35-2.58 (C-1'/C-1" proton) in the product **SFD_{1C} (6)**. This indicated the formation of thiazolidinone ring. The disappearance of chemical shift at δ205.1 for carbonyl group carbon and appearance of the signal at higher field at δ70.40 and an additional signal at δ4.22 for methylene proton further supported the formation of the thiazolidinone ring. The other signals were found comparable with that of the adduct **(5)**.

On the basis these spectral evidence, the structure of **SFD_{1C}** was formulated as *2,2-di[2-(4-chlorophenyl)-2-(3,4-dimethoxyphenyl)]ethyl] thiazolidin-4-one (6)*.



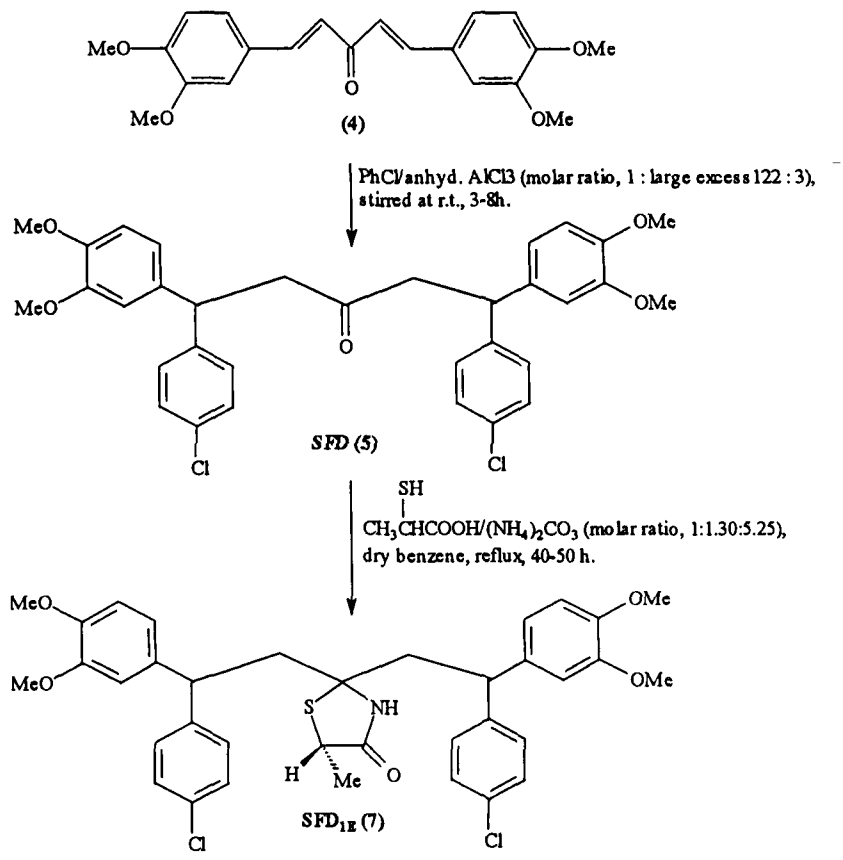
(6)

Synthesis of 2,2-di[2-(4-chlorophenyl)-2-(3,4-dimethoxyphenyl) ethyl]-5-(methyl)thiazolidin-4-one SFD_{1E} (7) from 1,5-bis(3,4-dimethoxyphenyl)pent-1,4-dien-3-one (4) via 1,5-bis(4-chlorophenyl)-1,5-bis(3,4-dimethoxyphenyl)pentan-3-one SFD (5) using 2-mercaptopropionic acid in the presence of ammonium carbonate.

The synthesis of compound SFD_{1E} (7) has been carried out as described above.

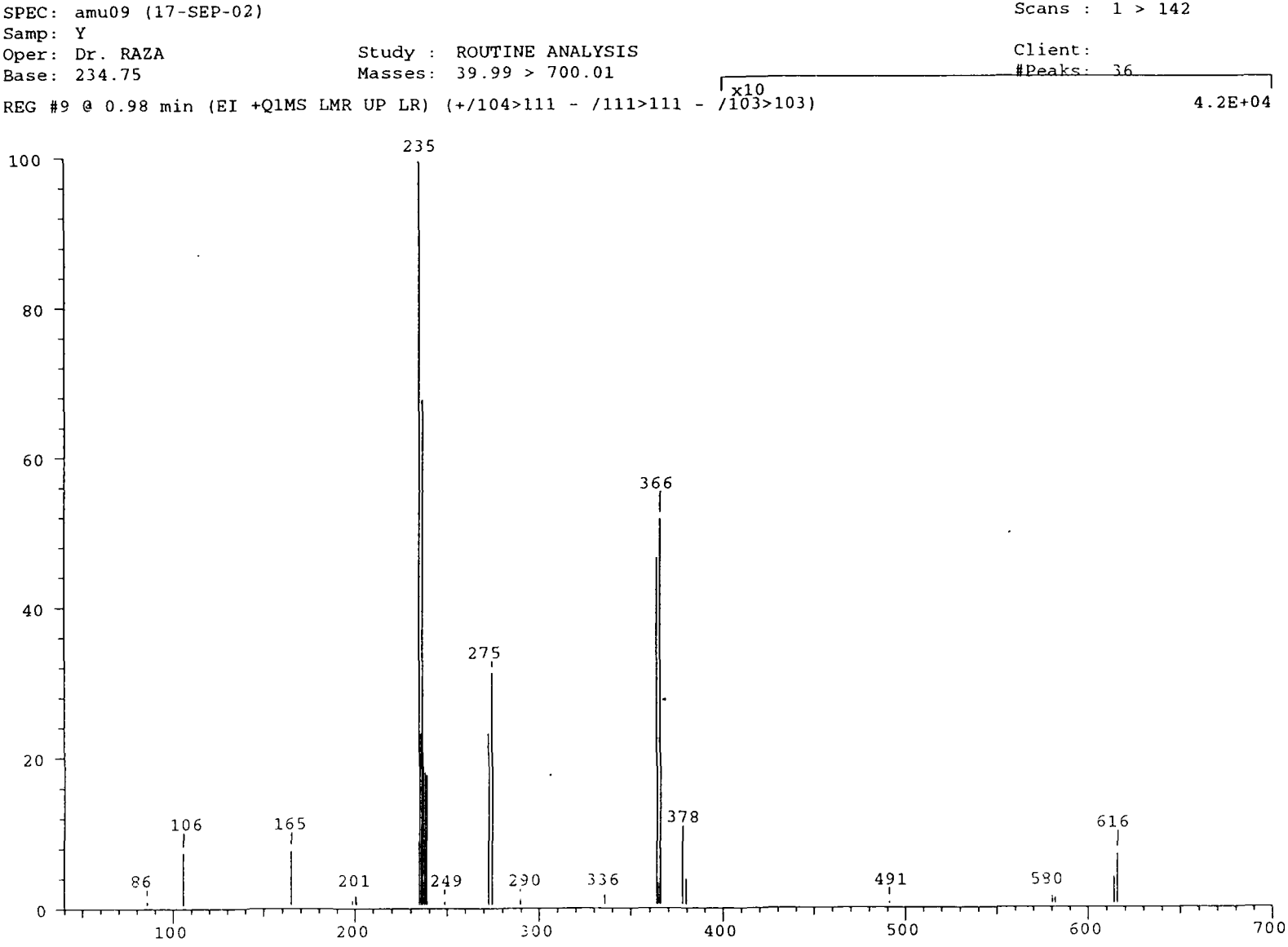
The adduct **SFD (5)** already prepared in SFD_{1C} (6) was treated with 2-mercaptopropionic acid and ammonium carbonate in dry benzene refluxing the reaction mixture for 40h with azeotropic removal of water. The products on purification over a silica gel column (pet. ether (40-60°)-diethyl ether, 7:3 v/v) and crystallisation (benzene-acetone, 8:2 v/v) yielded SFD_{1E} as white crystalline globules in 57% yield.

The outline of synthesis is presented below.



Structure Elucidation of SFD_{1E} (7)

It is a white crystalline globules solid, m.p. 208 °C and appears as light brown on exposure to iodine vapours (TLC). The structure of **SFD_{1E}** has been fully established by FT-IR, EI-MS, ^{1}H-NMR and by comparison with the spectral data of previously described similar compound **SFD_{1C} (6)**. The IR spectrum (KBr) showed characteristic absorption bands at 3453 (NH), 2900 (CH), 1681 (-CONH), 1593, 1485 (phenyl), 1435 (S-CH-CH_3), 1371, 1242, 1197, 1092, 1012, 810, cm^{-1}. In EI-MS spectrum of **SFD_{1E} (FIG. 17)** the molecular ion peak was absent but the fragment ions obtained **(CHART-5)**, confirmed its molecular weight 665/667/669 which is equal to the sum of the molecular weights of the adduct **(5)** (578), 2-mercaptopropionic acid (106) and ammonia (17) minus two molecules of water (36). This indicated that the formation of thiazolidinone ring has occurred by the cyclocondensation of the adduct **SFD (5)** with 2-mercaptopropionic acid and ammonia. The base peak at m/z 235/237 (100/68.18) with fragment ion [*p*-Cl $C_6H_4C_5H_2ONS]^+$ arised due to the cleavage of α- to the heterocyclic ring on the alkyl chain side of ring, indicated the location of ring. The mode of fragmentation is presented in **CHART-5**. The ^{1}H-NMR spectrum **(FIG. 18)** of **SFD_{1E} (7)** dissolved in $CDCl_3$ showed signals as assigned in **TABLE-6**. The assignments of all ^{1}H-NMR signals have been performed on the basis of typical chemical shift values, multiplicity and relative integrations and by comparison with ^{1}H-NMR spectrum of a previously described compound **SFD_{1C} (6)** (**TABLE-5**). The three doublets at δ2.29 (J=14.70 Hz, 4.50Hz), 2.46 (J=14.70Hz, 6.30Hz) and 4.72 (J=4.50Hz, 6.30Hz) were attributed to H_{up}-1'/H_{up}-1", H_{dn}-1'/H_{dn}-1" and H-2'/H-2" respectively. The signals at δ4.12-4.15 were accounted for four methoxyprotons. A doublet at δ1.54 (J=6.90Hz) was assigned to the methyl protons at C-5 of thiazolidinone ring and a quartet at δ3.83 (J=6.90Hz) for a proton of the same position. The proton signal were also found identical with that of **SFD_{1C}**.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Samp: Y
Oper: Dr. RAZA
Base: 234.75
Study : ROUTINE ANALYSIS
Masses: 39.99 > 700.01
Scans : 1 > 142
Client:
#Peaks: 36
REG #9 @ 0.98 min (EI +Q1MS LMR UP LR) (+/104>111 - /111>111 - /103>103)
x10
4.2E+04
235
366
275
106
165
378
616
86
201
249
290
336
491
580
100
80
60
40
20
0
100
200
300
400
500
600
700

FIG. 17

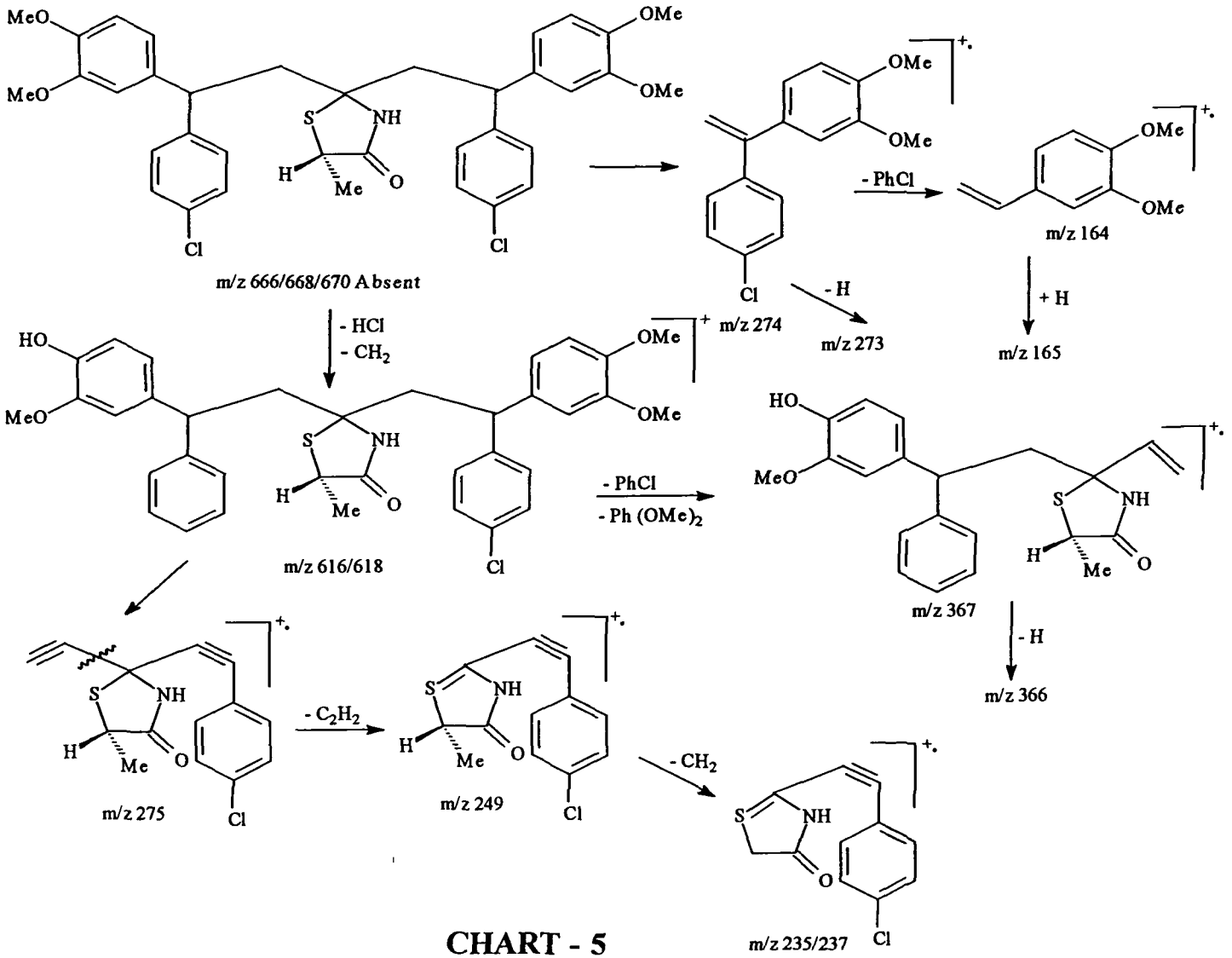
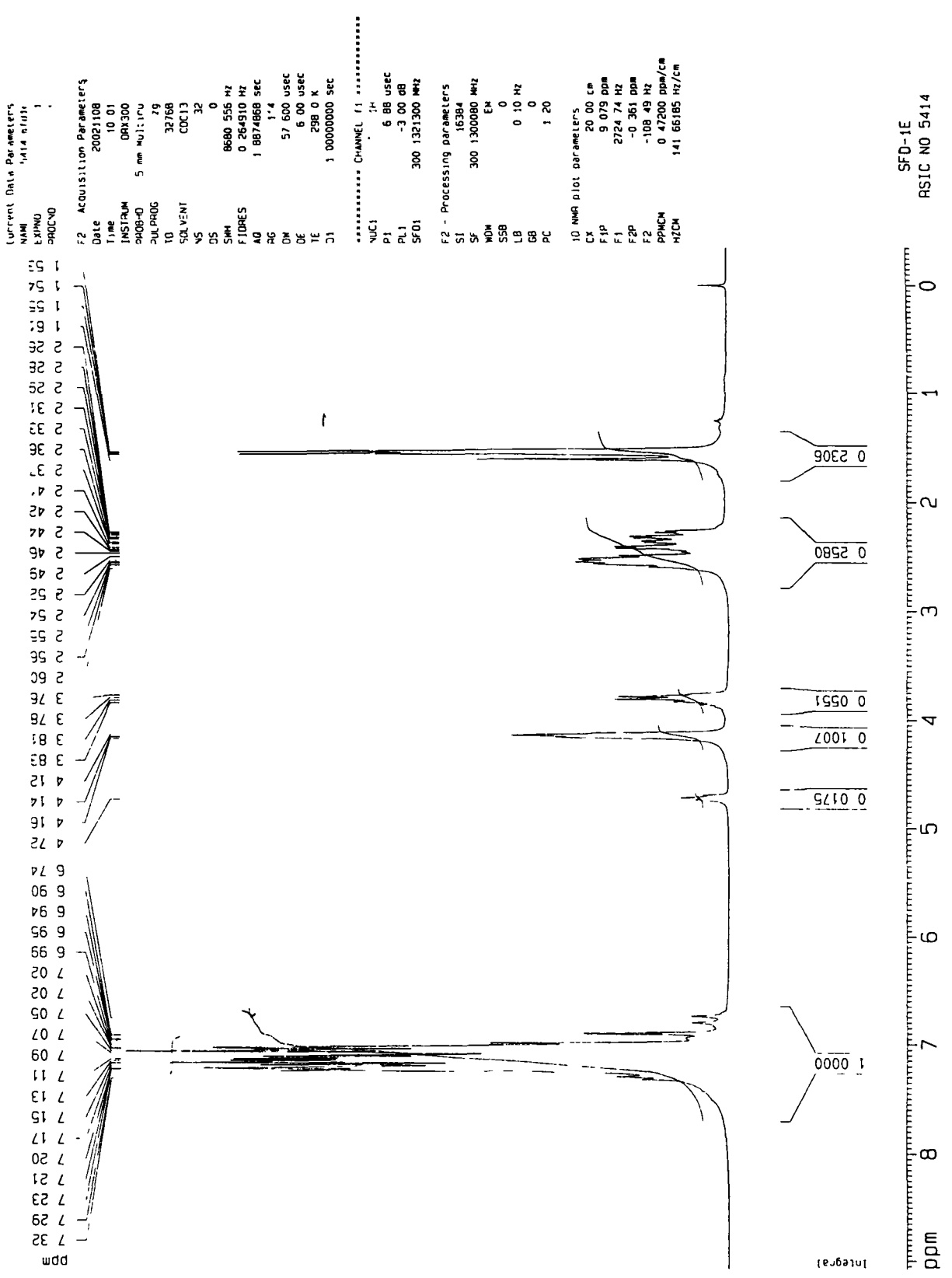

MeO
MeO
OMe
OMe
S
NH
H
Me
O
Cl
Cl
m/z 666/668/670 Absent
- HCl
- CH2
HO
MeO
m/z 616/618
- PhCl
- Ph (OMe)2
m/z 274
- H
m/z 273
- PhCl
m/z 164
+ H
m/z 165
m/z 367
- H
m/z 366
- C2H2
m/z 275
m/z 249
- CH2
m/z 235/237

CHART - 5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PROCNO
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SOLVENT CDCl3
NS 32
DS 0
SWH 8680 556 Hz
FIDRES 0 264910 Hz
AQ 1 8874868 sec
RG 1.4
DW 57 600 usec
DE 6 00 usec
TE 298 0 K
D1 1 00000000 sec
CHANNEL f1
NUC1 1H
P1 6 88 usec
PL1 -3 00 dB
SFO1 300 1321300 MHz
F2 - Processing parameters
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SF 300 1300080 MHz
WDW EM
SSB 0
LB 0 10 Hz
GB 0
PC 1 20
1D NMR plot parameters
CX 20 00 cm
F1P 9 079 ppm
F1 2724 74 Hz
F2P -0 361 ppm
F2 -108 49 Hz
PPMCM 0 47200 ppm/cm
HZCM 141 66185 Hz/cm
integral
1 0000
0 0175
0 1007
0 0551
0 2580
0 2306
SFO-1E
RSIC NO 5414
ppm

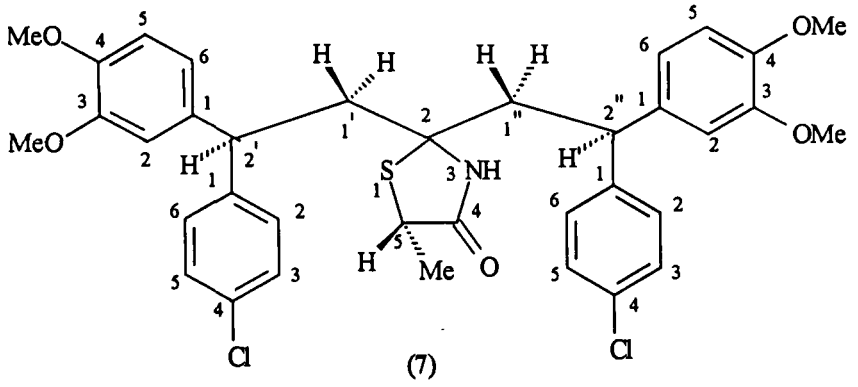
FIG. 18

Table - 6 : ^{1}H-NMR spectral data of SFD_{1E} (7)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)
1'up/1"up	2.29	2H	dd	$J_{1'up/1"up,1'dn/1"dn}$ = 14.70
				$J_{1'up/1"up,\ 2'/2"}$ = 4.50
1'dn/1"dn	2.46	2H	dd	$J_{1'up/1"up,1'dn/1"dn}$ = 14.70
				$J_{1'dn/1"dn,\ 2'/2"}$ = 6.30
2'/2"	4.72	1H	dd	$J_{1'up/1"up,\ 2'/2"}$ = 4.50
				$J_{1'dn/1"dn,\ 2'/2"}$ = 6.30
4 x OCH_3	4.12-4.15	12H	s	
H-5	3.83	1H	q	J = 6.90
5 - CH_3	1.54	3H	d	J = 6.90
4 x Ar	6.98-7.29	14H	br m	-

Note : Signal for NH, sometimes either merge with Ar signals or does not appear at all.

Based on the above facts, SFD_{1E} was characterized as *2,2-di[2-(4-chlorophenyl)-2-(3,4-dimethoxyphenyl)-ethyl]-5-(methyl)thiazolidin-4-one (7).*



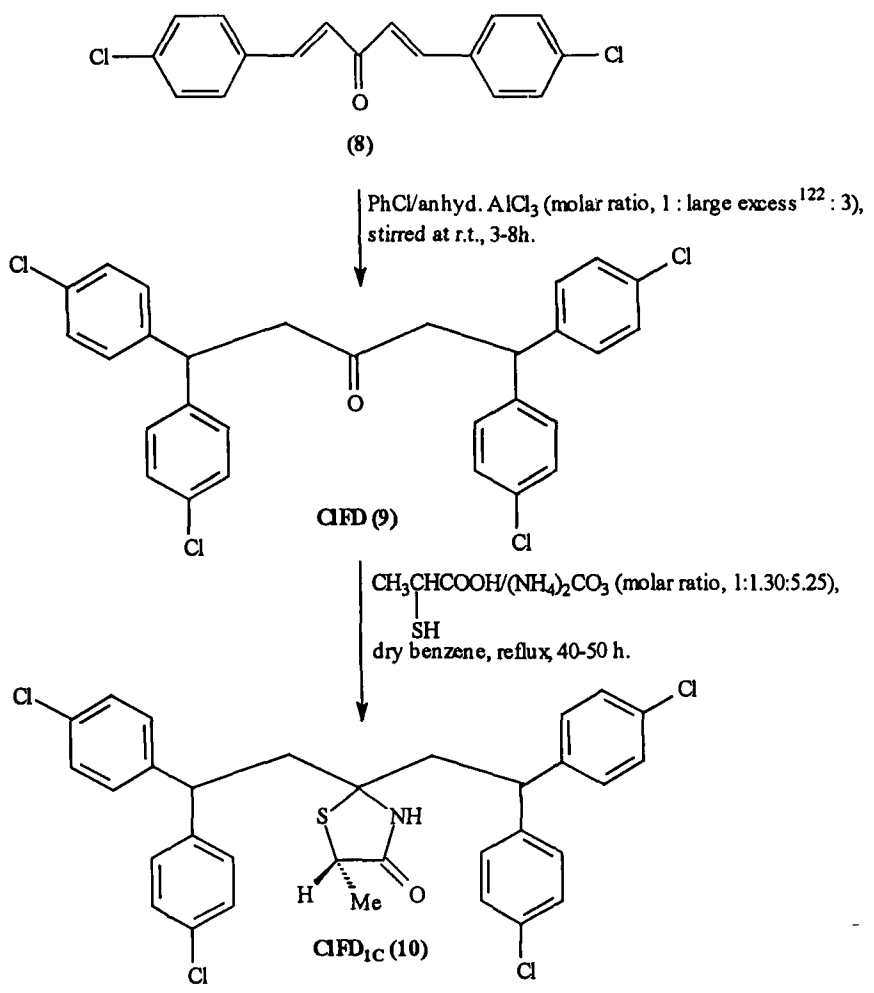
(7)

Synthesis of 2,2-di[2,2-bis(4-chlorophenyl)ethyl)-5-(methyl) thiazolidin-4-one $ClFD_{1C}$ (10) from, 1,5-bis(4-chlorophenyl) pent-1,4-dien-3-one(8) via, 1,1,5,5-tetra(4-chlorophenyl)pentan-3-one ClFD (9) using 2-mercapto propionic acid in the presence of ammonium carbonate

The synthesis of **$ClFD_{1C}$ (10)** was carried out as described above.

The adduct **ClFD (9)** was first prepared by treating a solution of 1,5-bis(4-chlorophenyl)pent-1,4-dien-3-one **(8)** with anhydrous aluminium chloride (molar ratio, 1:3) in excess chlorobenzene as yellow semi solid mass in 76% yield. The adduct **ClFD (9)** in dry benzene was then reacted with 2-mercaptopropionic acid and ammonium carbonate. The products on purification over a silica gel column (pet. ether (40-60°)-diethyl ether, 7:3 v/v) and crystallization (benzene-acetone, 8:2 v/v) afforded **$ClFD_{1C}$ (10)** as white crystalline globules in 56% yield.

The outline of synthesis is given below.



Structure Elucidation of ClFD (9)

It is a yellow semi-solid mass and appears light brown on exposure to iodine vapours (TLC). The structure of ClFD has been established by FT-IR, FAB-MS, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum (KBr) displayed characteristic bands at 2924 (C-H), 1710 (C=O), 1592, 1572, 1490 (phenyl), 1408, 1095, 1059, 1008, 819, 747 cm^{-1}. The FAB-MS spectrum (**FIG. 19**) of **ClFD (9)** showed a set of $[M+H]^+$ peaks at m/z 527/529/531/533/535, confirming its molecular weight 526/528/530/532/534 [$C_{29}H_{22}OCl_4$] which is equal to the sum of the molecular weights of *1,5-bis(4-chlorophenyl)pent-*

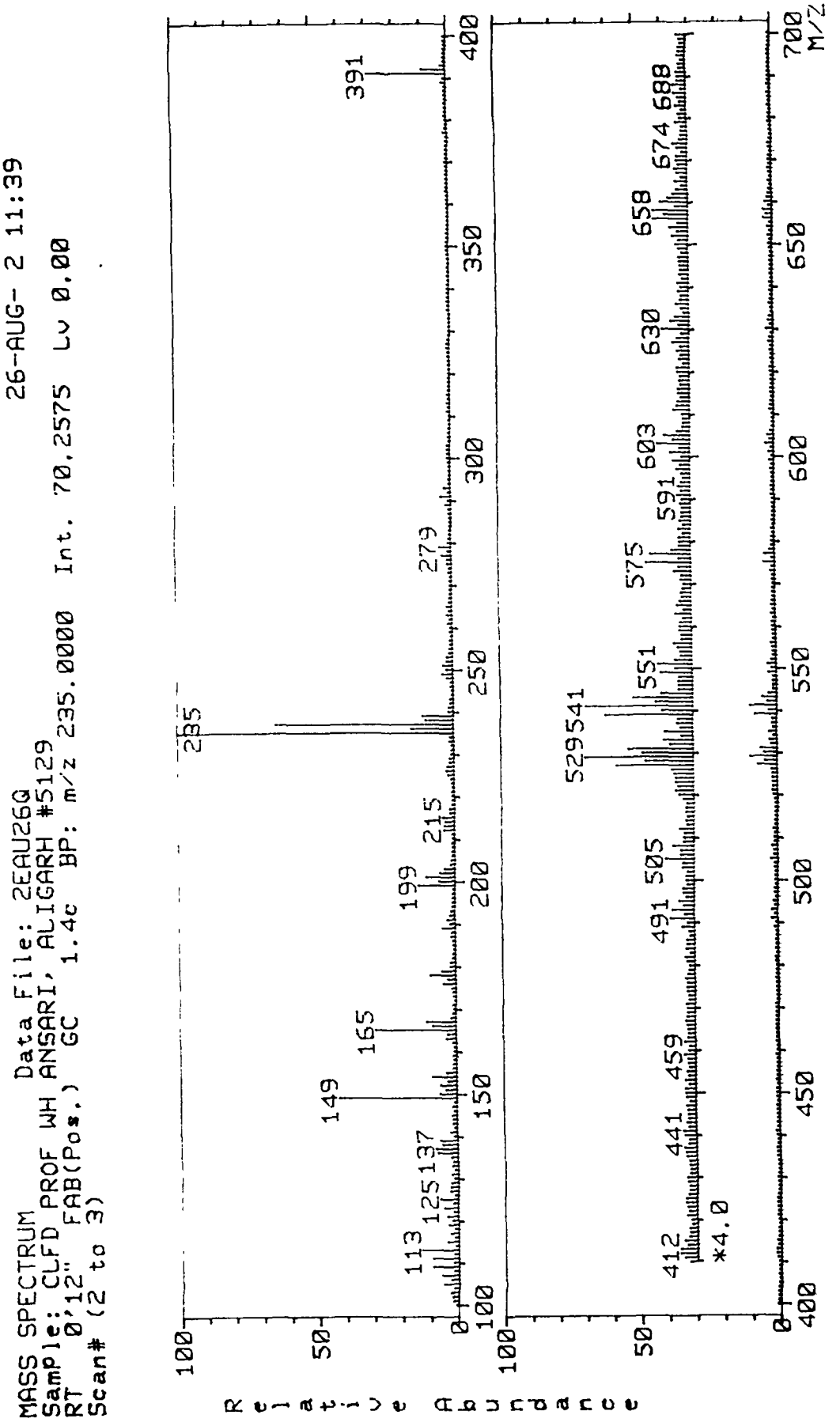

MASS SPECTRUM Data File: 2EAU26Q
Sample: CLFD PROF WH ANSARI, ALIGARH #5129
RT 0'12" FAB(Pos.) GC 1.4c BP: m/z 235.0000 Int. 70.2575 Lv 0.00
Scan# (2 to 3)
26-AUG- 2 11:39
Relative Abundance
M/Z
*4.0

FIG. 19

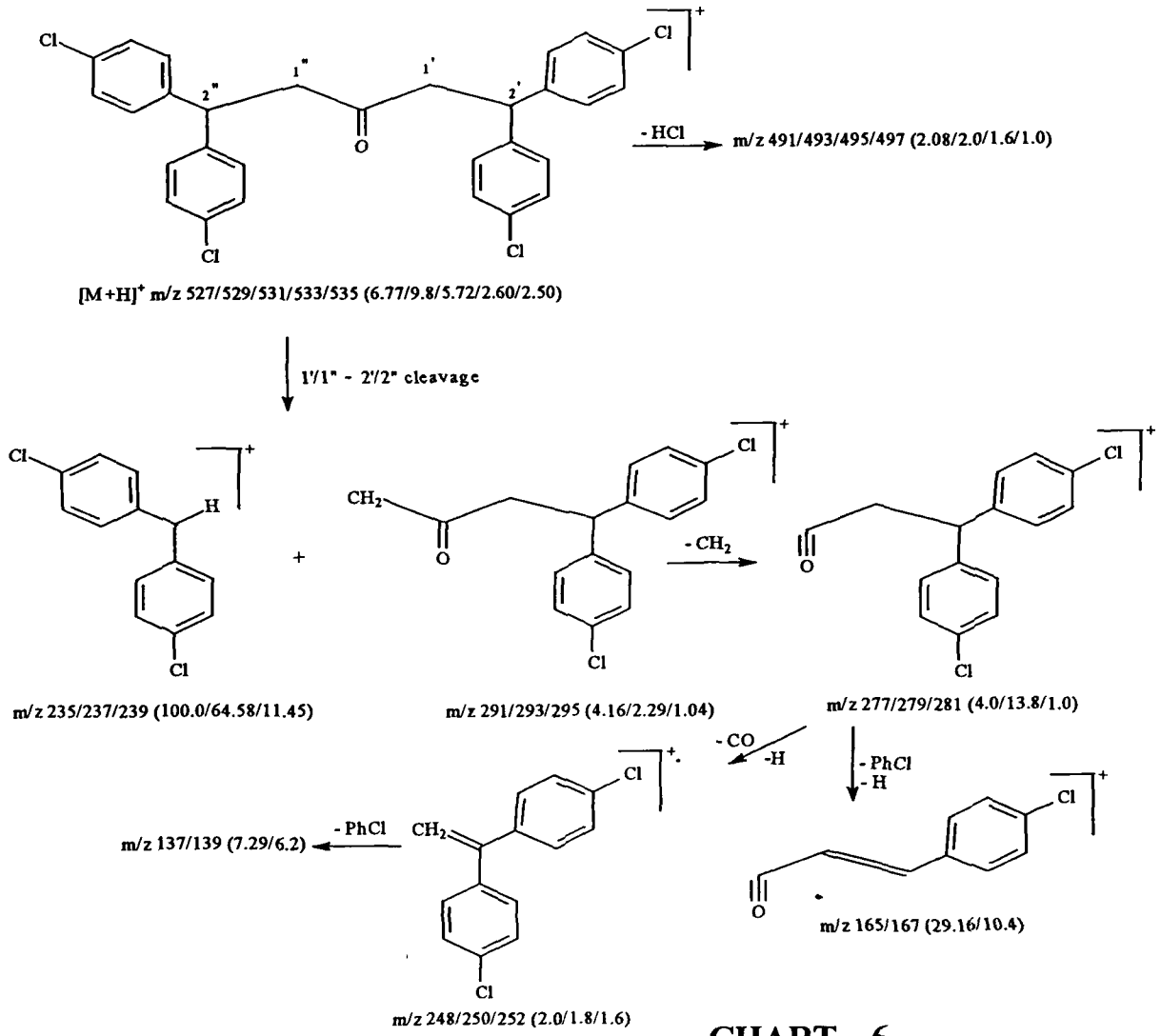
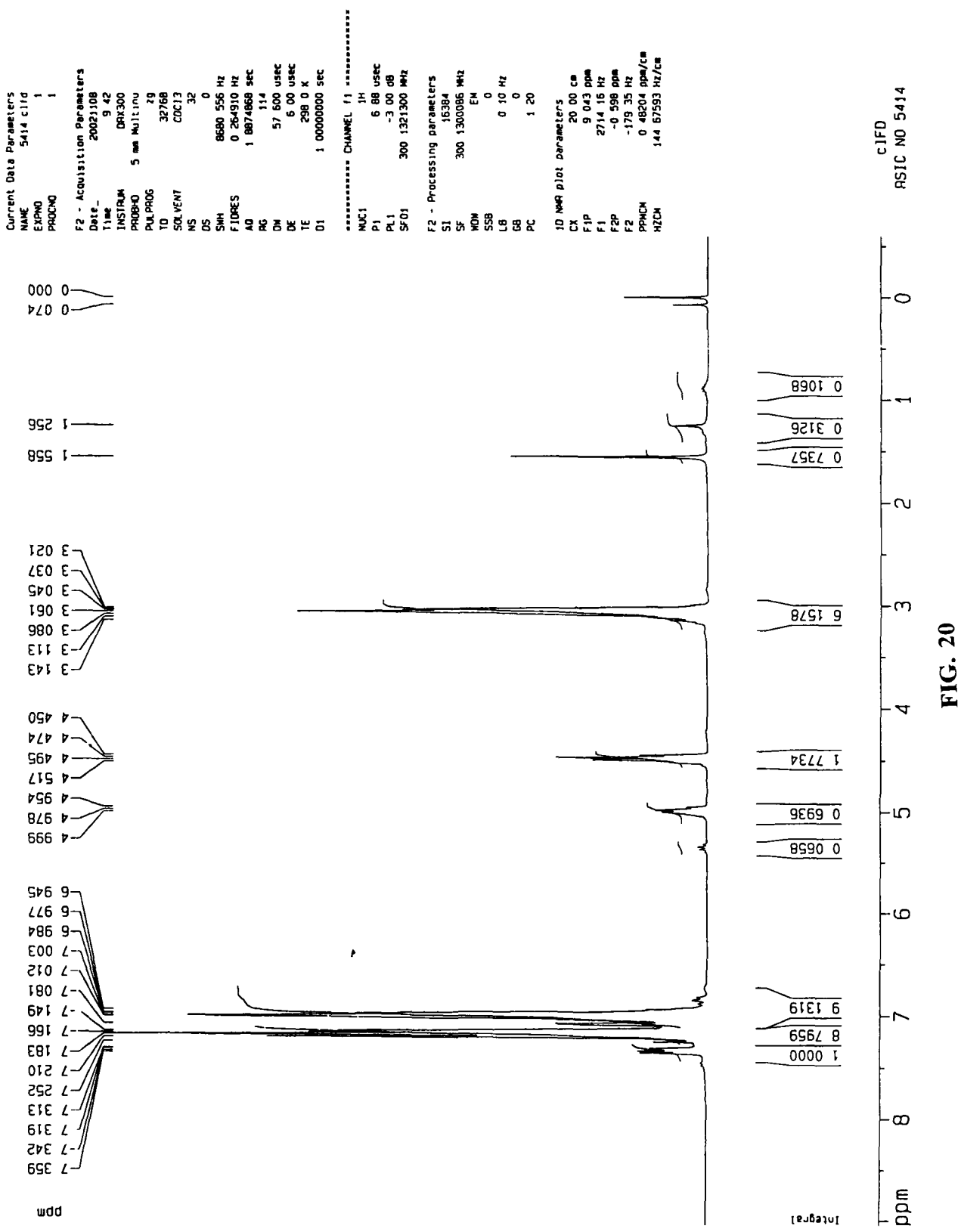

- HCl
m/z 491/493/495/497 (2.08/2.0/1.6/1.0)
[M+H]+ m/z 527/529/531/533/535 (6.77/9.8/5.72/2.60/2.50)
1'/1" - 2'/2" cleavage
m/z 235/237/239 (100.0/64.58/11.45)
m/z 291/293/295 (4.16/2.29/1.04)
- CH2
m/z 277/279/281 (4.0/13.8/1.0)
- CO
-H
- PhCl
- H
m/z 165/167 (29.16/10.4)
- PhCl
m/z 137/139 (7.29/6.2)
m/z 248/250/252 (2.0/1.8/1.6)

CHART - 6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PROCNO 1
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PULPROG zg
TD 32768
SOLVENT CDCl3
NS 32
DS 0
SWH 8680 556 Hz
FIDRES 0 264910 Hz
AQ 1 8874868 sec
RG 114
DW 57 600 usec
DE 6 00 usec
TE 298 0 K
D1 1 00000000 sec
CHANNEL f1
NUC1 1H
P1 6 88 usec
PL1 -3 00 dB
SFO1 300 1321300 MHz
F2 - Processing parameters
SI 16384
SF 300 1300086 MHz
WDW EM
SSB 0
LB 0 10 Hz
GB 0
PC 1 20
1D NMR plot parameters
CX 20 00 cm
F1P 9 043 ppm
F1 2714 15 Hz
F2P -0 598 ppm
F2 -179 35 Hz
PPMCM 0 48204 ppm/cm
HZCM 144 67593 Hz/cm
c1FD
ASIC NO 5414
ppm
Integral
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0 3126
0 7357
6 1578
1 7734
0 6936
0 0658
9 1319
8 7959
1 0000

FIG. 20

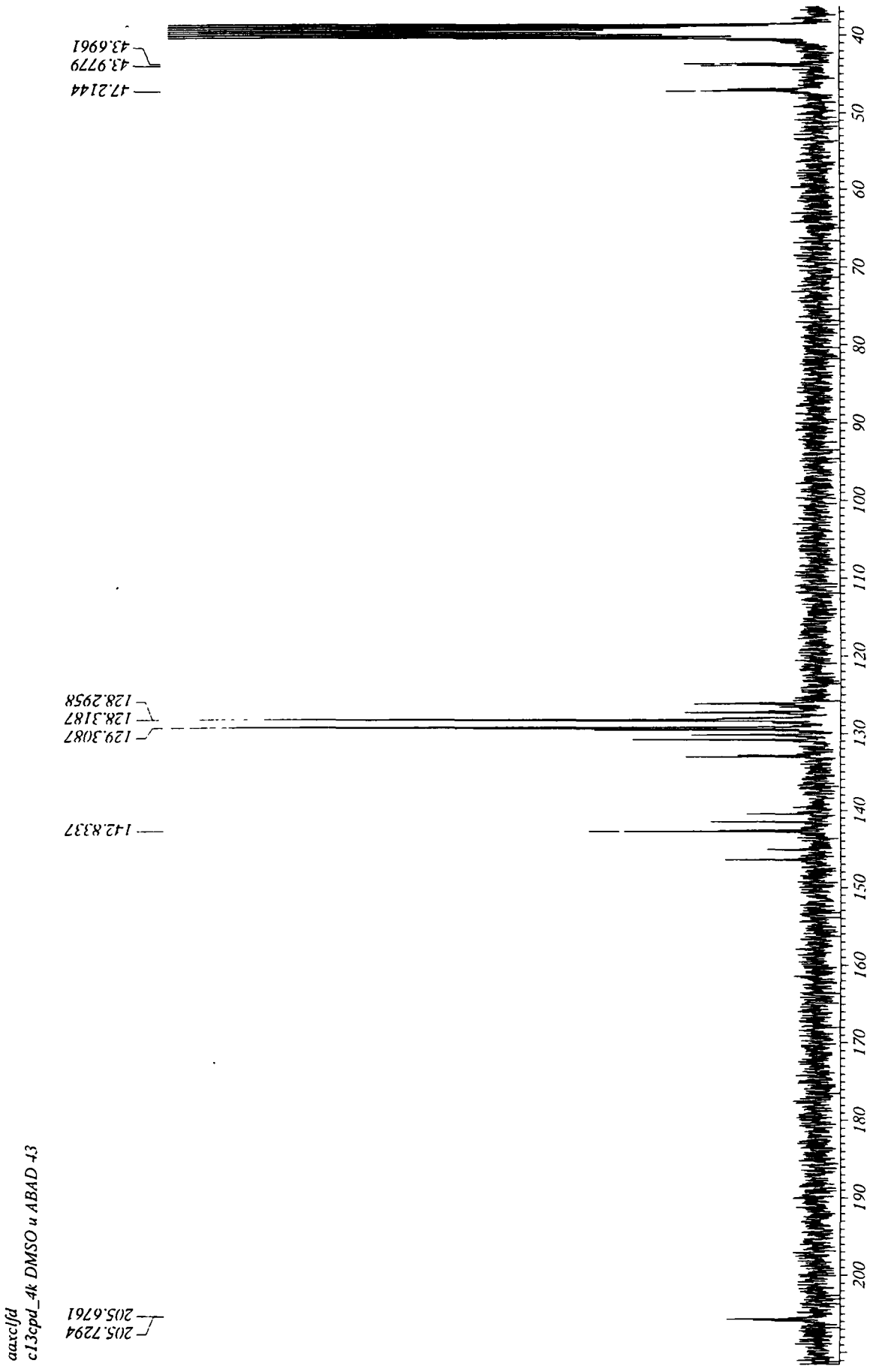

aaxcljd
c13cpd_4k DMSO u ABAD 43
205.6761
205.7294
142.8337
129.3087
128.3187
128.2958
47.2144
43.9779
43.6961
(ppm)

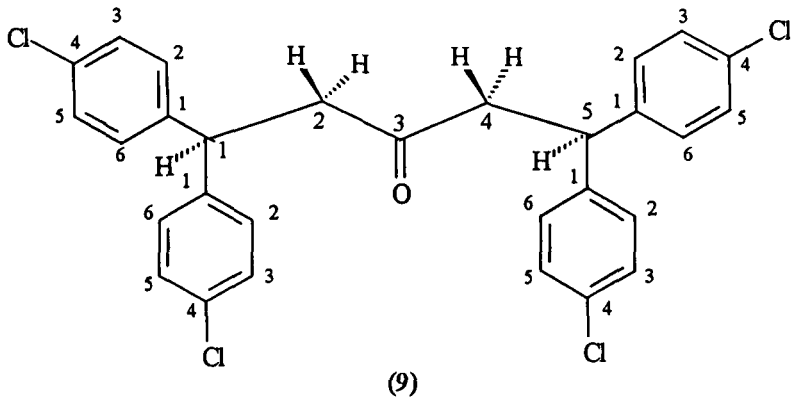
FIG. 21

TABLE -7 : ^{1}H-NMR and ^{13}C-NMR spectral data of ClFD (9)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)	C-nr	δ(ppm)
2up/4up	3.02	2H	dd	$J_{2up/4up,2dn/4dn}$=17.10	2/4	43.98
				$J_{2up/4up,1/5}$=9.90		
2dn/4dn	3.14	2H	dd	$J_{2up/4up,2dn/4dn}$=17.10	1/5	47.21
				$J_{2dn/4dn,1/5}$=4.80		
1/5	4.49	2H	dd	$J_{2up/4up,1/5}$=9.90	3	205.67
				$J_{2dn/4dn,1/5}$=4.80		
4 x Ar	6.95-7.36	16H	br m	-	4 x Ar	128.29 - 142.83

1,4-dien-3-one (302) and two molecules of chloro- benzene (224). This indicated that the formation of the adduct has occurred by the addition of two molecules of chlorobenzene to the diene. The base peak at m/z 235/237/239 (100.0/64.58/11.45) and other significant peaks at m/z 249/251/253 (3.7/2.4/ 2.08), 165/167 (29.16/10.41) were shown in the fragmentations (**CHART-6**). The ^{1}H-NMR (**FIG. 20**) and ^{13}C-NMR (**FIG. 21**) spectra of **ClFD** dissolved in $CDCl_3$ showed signals as assinged in **TABLE-7**. The assignments of all ^{1}H- and ^{13}C-NMR signals to individual H- and C-atoms have been performed on the basis of typical chemical shift values, multiplicity, relative integrations and also by comparison with the spectra of previously described adduct **SFD (5)**. The two double doublets at δ3.02 (J=17.10 Hz,J=9.90 Hz) and δ3.14 (J=17.10 Hz, J=4.80 Hz) were attributed to H-2up/H-4up and H-2dn/H-4dn. A double doublet at δ4.49 (J=9.90 Hz, J=4.80 Hz) was assigned to H-1/5 proton. Thus, the coupling constants showed that two diastereotopic hydrogens at C-2/C-4 are anti- and synperiplanars with C-1/C-5 hydrogen. The aromatic protons signals were accounted for sixteen protons of four benzene rings. The ^{13}C-NMR spectrum showed signals as assigned (**TABLE-7**). A signal at δ43.98 was assigned to C-2/C-4 and at δ47.21 to C-1/C-5 carbons. The peak at δ205.67 was attributed to carbonyl carbon and the signals for the aromatic carbons were observed at δ128.29-142.83.

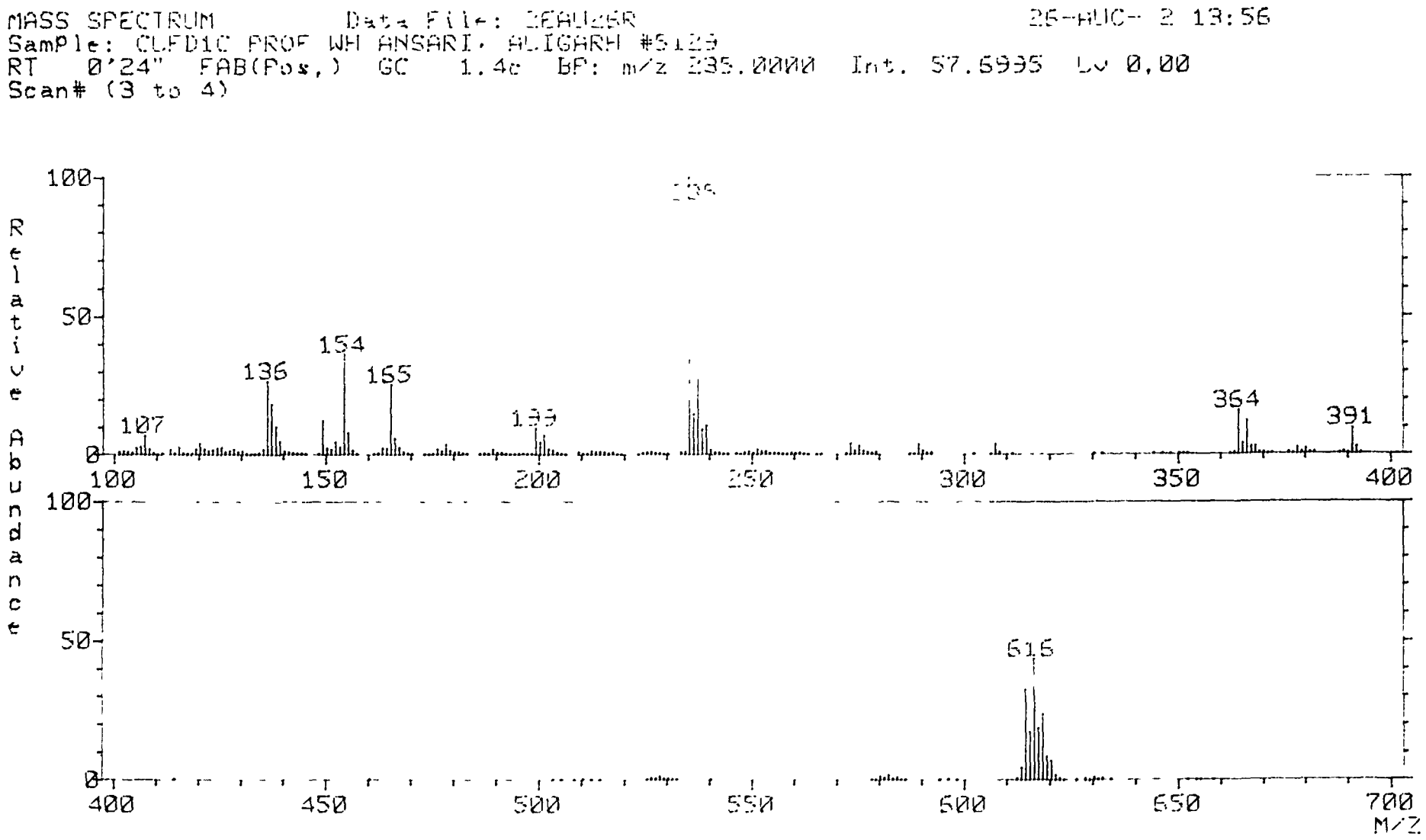
On the basis of above facts, the structure of **ClFD** was formulated as *1,1,5,5-tetra(4-chlorophenyl)pentan-3-one(9)*.



(*9*)

Structue Elucidation of $ClFD_{1C}$ (10)

It is a white globules shaped crystalline solid, m.p 168°C and appears brown on exposure to iodine vapours (TLC). The constitution of **$ClFD_{1C}$** has been established by FT-IR, FAB-MS, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum (KBr) showed characteristic absorption band at 3425 (NH), 2909 (CH), 1680 (-CONH), 1591, 1484 (phenyl) 1450 (S-CH-CH_3), 1435 (C-N) cm^{-1}. The FAB mass spectrum (Argon/Xenon as the FAB gas) **(FIG. 22)** of **$ClFD_{1C}$** showed a set of $[M+1]^+$ peaks at m/z 614/616/618/620/622, comfirming its molecular weights 613/615/617/619/621 which is consistent with the molecular formula $C_{32}H_{27}ONSCl_4$. The other significant peaks were observed at m/z 364/366/368 and 235/237/239 (**CHART-7**). The ^{1}H-NMR **(FIG. 23)** and ^{13}C-NMR **(FIG. 24)** spectra of **$ClFD_{1C}$** dissolved in $CDCl_3$ showed signals as assigned in **TABLE-8**. The assignments of all ^{1}H- and ^{13}C-NMR signals to individual H- and C-atoms have been performed on the basis of their typical chemical shift values, their multiplicities, relative integrations and by comparison with the ^{1}H- and ^{13}C-NMR spectra of previously described similar compounds **(3)** and **(6)** **(TABLES 2, 3, 5 and 6)**. The ^{1}H-NMR spectrum is in agreement with the formation of thiozolidinone ring as the chemical shift of C-2/C-4 protons in **ClFD** has shifted upfiled from δ3.02-3.14 to δ2.30-2.42 (1' and 1" in **$ClFD_{1C}$**) due to the ring formation. A quartet at δ3.81 (J=6.6Hz) and a doublet at δ1.56 (J=6.6 Hz) were attributed to a proton and a methyl group protons at C-5 of thiazolidinone ring. The ^{13}C-NMR spectrum showed a signal at δ49.50 which was assigned to C-1'/C-1" carbon and an another signal at δ46.62 to C-2'/C-2" carbon. The ^{13}C-NMR spectrum is also in agreement with a thiazolidinone ring as C-3 signalof carbonyl carbon has shifted to higher field from δ205.67 to δ175.29 due to disappearance of C=O group and formation of ring. A signal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Sample: CLFD1C PROF WH ANSARI, ALIGARH #5129
RT 0'24" FAB(Pos,) GC 1.4e BP: m/z 235.0000 Int. 57.6935 Lv 0,00
Scan# (3 to 4)
Relative Abundance
100
50
0
107
136
154
155
133
364
391
515
100
150
200
250
300
350
400
450
500
550
600
650
700
M/Z

FIG. 22

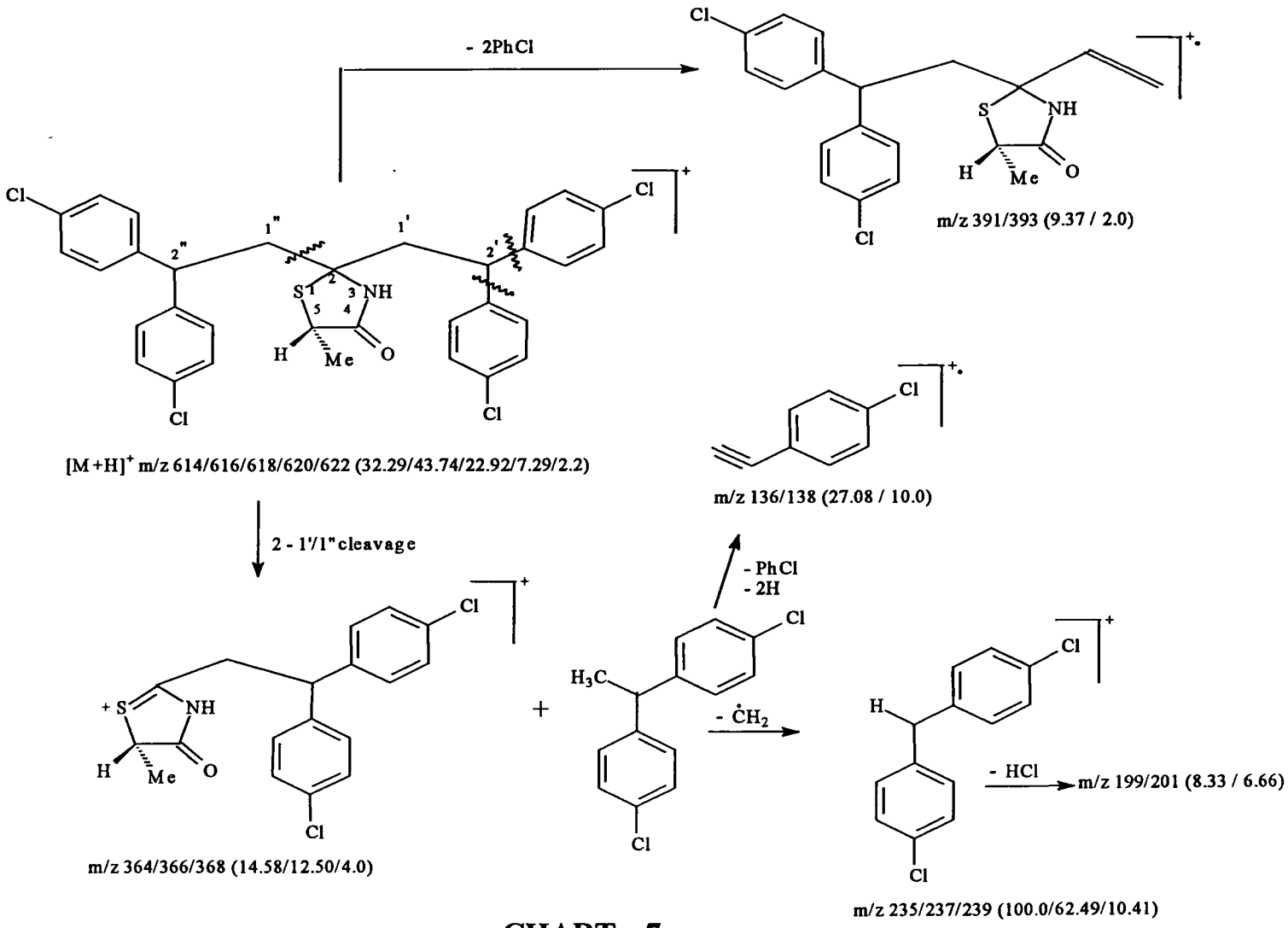
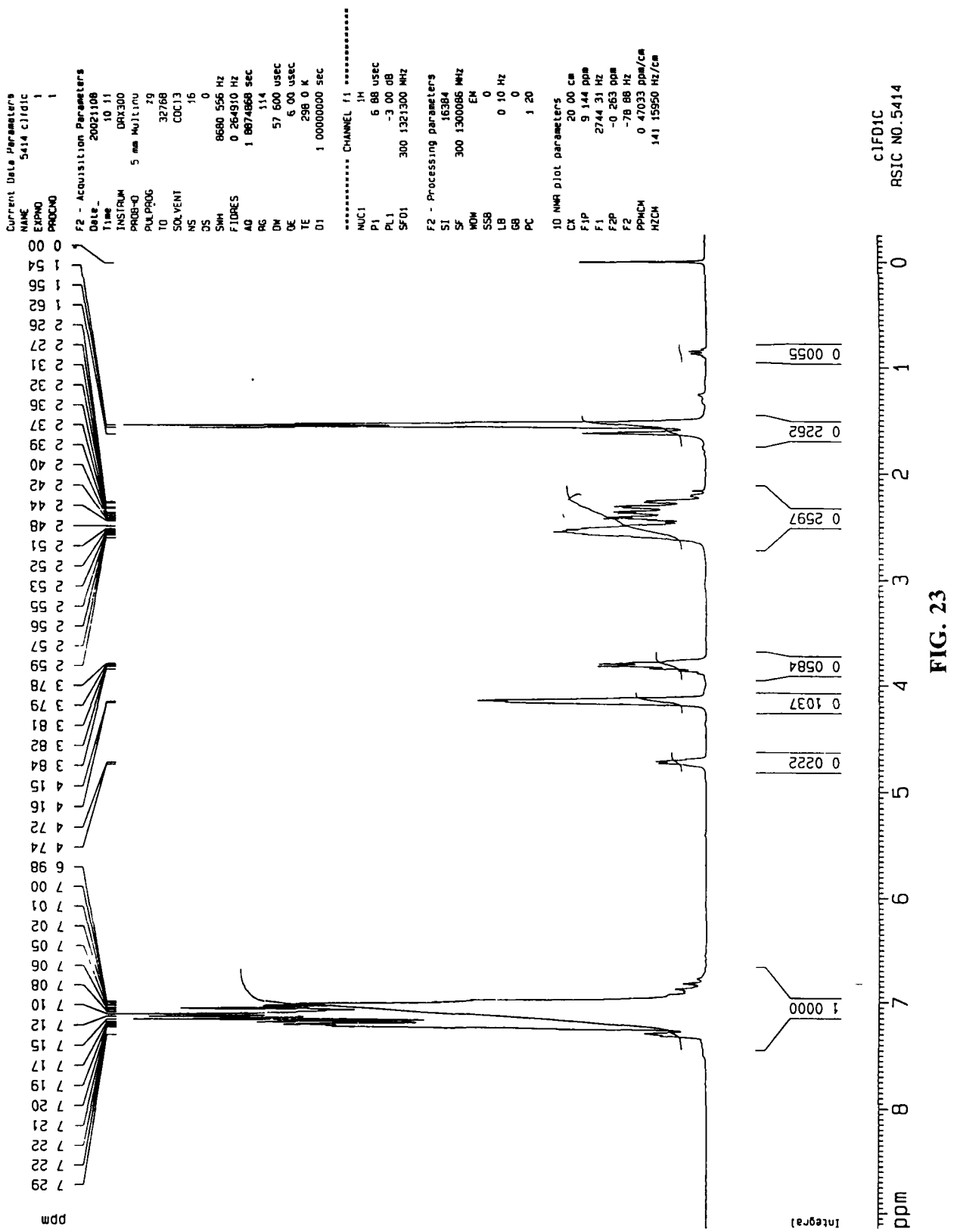

- 2PhCl
m/z 391/393 (9.37 / 2.0)
[M+H]+ m/z 614/616/618/620/622 (32.29/43.74/22.92/7.29/2.2)
m/z 136/138 (27.08 / 10.0)
2 - 1'/1" cleavage
- PhCl
- 2H
- ĊH2
- HCl
m/z 199/201 (8.33 / 6.66)
m/z 364/366/368 (14.58/12.50/4.0)
m/z 235/237/239 (100.0/62.49/10.41)

CHART - 7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SOLVENT CDCl3
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FIDRES 0.264910 Hz
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RG 114
DW 57.600 usec
DE 6.00 usec
TE 298.0 K
D1 1.00000000 sec
CHANNEL f1
NUC1 1H
P1 6.88 usec
PL1 -3.00 dB
SFO1 300.1321300 MHz
F2 - Processing parameters
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SF 300.1300086 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.20
1D NMR plot parameters
CX 20.00 cm
F1P 9.144 ppm
F1 2744.31 Hz
F2P -0.263 ppm
F2 -78.88 Hz
PPMCM 0.47033 ppm/cm
HZCM 141.15950 Hz/cm
1.0000
0.2597
0.2262
0.0055
0.0584
0.1037
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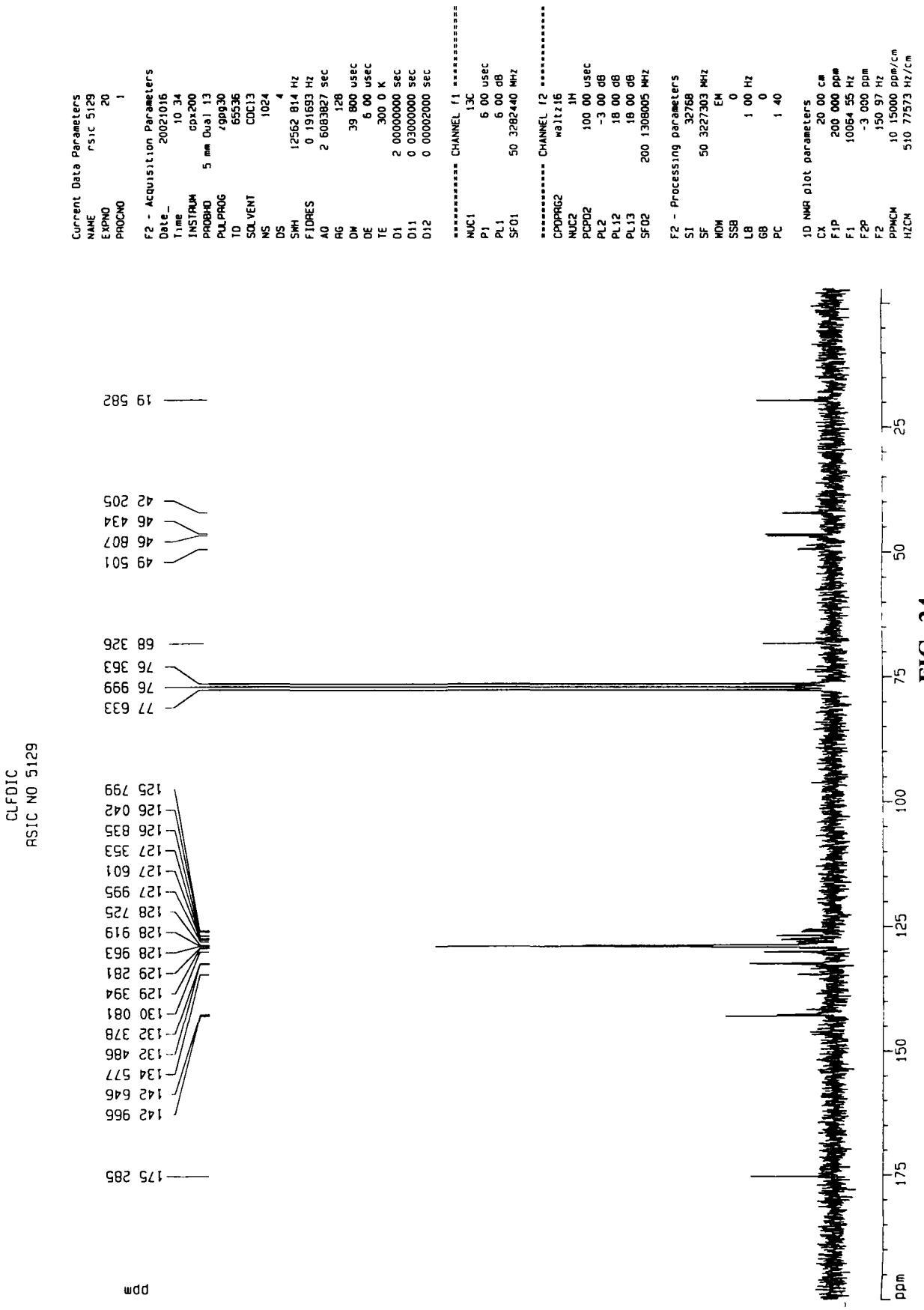
Integral
ppm
c1FD1C
RSIC NO.5414

FIG. 23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PROCNO 1
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PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 12562 814 Hz
FIDRES 0 191693 Hz
AQ 2 6083827 sec
RG 128
DW 39 800 usec
DE 6 00 usec
TE 300 0 K
D1 2 00000000 sec
D11 0 03000000 sec
D12 0 00002000 sec
CHANNEL f1
NUC1 13C
P1 6 00 usec
PL1 6 00 dB
SF01 50 3282440 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100 00 usec
PL2 -3 00 dB
PL12 18 00 dB
PL13 18 00 dB
SF02 200 1308005 MHz
F2 - Processing parameters
SI 32768
SF 50 3227303 MHz
WDW EM
SSB 0
LB 1 00 Hz
GB 0
PC 1 40
1D NMR plot parameters
CX 20 00 cm
F1P 200 000 ppm
F1 10064 55 Hz
F2P -3 000 ppm
F2 150 97 Hz
PPMCM 10 15000 ppm/cm
HZCM 510 77573 Hz/cm
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25
50
75
100
125
150
175
19 582
42 205
46 434
46 807
49 501
68 326
76 363
76 999
77 633
125 799
126 042
126 835
127 353
127 601
127 995
128 725
128 919
128 963
129 281
129 394
130 081
132 378
132 486
134 577
142 646
142 966

FIG. 24

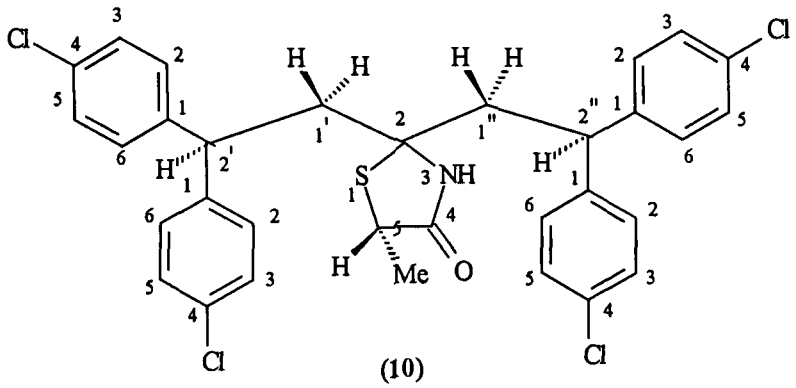
Table -8 : ^{1}H-NMR and ^{13}C-NMR spectral data of $ClFD_{1C}$ (10)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)	C-nr	δ(ppm)
1'up/1"up	2.30	2H	dd	$J_{1'up/1"up,1'dn/1"dn}$ = 16.20	1'/1"	49.50
				$J_{1'up/1"up,\ 2'/2"}$ = 4.20		
1'dn/1"dn	2.42	2H	dd	$J_{1'up/1"up,1'dn/1"dn}$ = 16.20		
				$J_{1'dn/1"dn,\ 2'/2"}$ = 7.20		
2'/2"	4.16	1H	dd	$J_{1'up/1"up,2'/2"}$ = 4.20	2'/2"	46.62
				$J_{1'dn/1"dn,\ 2'/2"}$ = 7.20	2	68.32
H-5	3.81	1H	q	J = 6.60	5	42.21
5-CH_3	1.56	3H	d	J = 6.60	5-CH_3	19.58
NH	7.29	1H	s	-	4	175.29
4 x Ar	6.98-7.22	16H	br m	-	4 x Ar	125.80-142.97

Note : Signal for NH, sometimes either merge with Ar signals or does not appear at all.

at δ19.58 was assigned to methyl carbon and the signals for aromatic carbons were observed at δ125.80-143.97.The ^{1}H- and ^{13}C-NMR signals were found comparable with that of similar compounds (3) and (6).

Based on the above spectral evidence compound **ClFD$_{1C}$** was characterised as *2,2-di[2,2-bis(4-chlorophenyl)ethyl]-5-(methyl)thiazolidin-4-one (10)*.



(10)

Experimental

EXPERIMENTAL

Reagents and solvents were of commercial grade and were used without further purification. All melting points were determined on a Koffler hot-plate apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 621 spectrophotometer in KBr-pellets. FTIR were recorded on Perkin-Elmer spectrophotometer RX_1 and wave numbers (υ_{max}) were recorded in cm^{-1}. ^{1}H-NMR spectra were recorded in Brucker Ac300, Brucker DRX 300 and Varian Unity 400 in $CDCl_3$, DMSO-d_6 and acetone-d_6, with TMS as the internal standard . The abbreviations s, d, t, m, dd, ddd, brp, dt denote singlet, doublet, triplet, multiplet, double doublet, triple doublet, broad pentet and double triplet. ^{13}C-NMR were recorded on a Varian Unity 75 and 100 spectrometers. EIMS were recorded on V.G. Micromass model ZAB-IF apparatus at 70ev ionisation voltage. DCI-Mass spectra were recorded on a Ribermag R10-10B quadrupole mass spectrometer, using ammonia as reagent gas. The FAB mass spectra were recorded on a JEOL SX 102/DA-6000 Mass spectrometer/Data system using Argon/Xenon (6KV, 10mA) as the FAB gas. The accelerating voltage was 10KV and the spectra were recorded at room temperature. *m*-nitrobenzyl alcohol (NBA) was used as the matrix. HRMS values were recorded in quadrupole-time of flight mass spectrometer (Qtof2, Micromass, Manchester, UK) equipped with a standard electrospray ionisation (ESI) interface. Samples were dissolved in acetone (p.a.) **P (2)** 1.2 mg mL^{-1}, $\mathbf{E_{1A}(3)}$, 1.0 mg mL^{-1}) and diluted 1/10 in methanol (HPLC grade) containing 0.1% of acetic acid. Using a Hardvard syringe pump (model 22) these solutions were infused at flow rate of 1μL min^{-1}. To enhance the $[M+Na]^+$ signals of **P (2)** 10 μL of NaI solution (2μg/μL in 50:50 isopropyl alcohol/H_2O) was added. Thin layer chromatography (TLC) was carried out on

0.25 mm layer plates with silica gel 'G' (Merck). Spots were visualised on exposure to iodine vapours using iodine chamber. The column chromatography was performed on silica gel [Merck (60-120) mesh] using 25-30 g per g. of material to be separated and purified. Solvents were dried according to standard procedures.

4,4'-Dichlorochalcone (1)

4,4'-Dichlorochalcone (1) was prepared following a published but slightly modified procedure[122] by condensing *p*-chloroacetophenone with *p*-chlorobenzylidene diacetate (both prepared according to reported procedures[123]) in equimolar ratio in the presence of 2.5 equivalents of sodium hydroxide. A mixture of *p*-chloroacetophenone (4.13g, 0.0268 mol) and *p*-chorobenzylidene diacetate (6.5g 0.0268 mol) in ethanol (21 ml) was kept on an ice bath in a 500 ml flask. To this was added sodium hydroxide (2.68g, 0.0671 mol, 10%) dropwise with stirring. After complete addition, the reaction mixture was furhter stirred for 3 h, then diluted with 300 ml of ice cold water and kept in refrigerator overnight. The precipitate formed was filtered and washed successively with water to make it neutral. It was finally washed with 10 ml of cold alcohol and the yellow solid mass thus obtained was crystallised from acetone-benzene to give (1) as light yellow crystalline needles, 6.29 g (85%), m.p. 156°C, Rf 0.72 (pet. ether (40-60°)-benzene, 1:1 v/v).

1,3,3-Tris(4-chlorophenyl)propan-1-one P (2)

It was prepared following a reported method[122]. To a suspension of 4,4'-dichlorochalcone (1) (990 mg, 3.57 mmol) and anhydrous aluminium chloride (1450 mg, 10.9 mmol) in chlorobenzene (8 ml), chlorobenzene (25 ml) was added slowly with stirring at room temperature. After complete addition, the

reaction mixture was stirred for 2 h. The resulting yellow solution was extracted with ethyl acetate, washed several times with water, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The products on crystallization from benzene yielded **P (2)** as white crystalline needles, 920 mg (66%), m.p. 155°C, Rf 0.58 (pet. ether (40-60°)-benzene, 9:1 v/v).

Spectral data of P (2) :

IR (KBr pellet) : υ_{max} cm^{-1} 1677 (C=O), 2927 (CH), 1590 (phenyl), 1485, 1400, 1264, 1209, 1090, 1013, 838, 774.

^{1}H-NMR (acetone-d_6, 400 MHz, temp. 30°C) : δ_H 8.04 (2H, d, J=8.69Hz, Ar-H-2,6), 7.51 (2H, d, J=8.69 Hz, Ar-H-3,5), 7.39 (4H,d,J=8.69Hz, Ar'/Ar'-H-3,5), 7.28(4H, d, J=8.69Hz, Ar'/Ar'-H-2,6), 4.78 (1H, t, J=7.32 Hz, H-3), 3.92 (2H, d, J=7.32 Hz, H-2).

^{13}C-NMR (100 MHz, acetone-d_6, temp. 30°C) : δ_C 196.95 (C-1), 144.09 (C-Ar'/Ar'-1), 139.68 (C-Ar-4), 136.66 (C-Ar-1), 132.56 (C-Ar'/Ar'-4), 130.68 (C-Ar-2,6), 130.47 (C-Ar'/Ar'-2,6), 129.64 (C-Ar-3,5), 129.32 (C-Ar'/Ar'-3,5), 45.77 (C-3), 44.58 (C-2).

DCI-MS (NH_3) : m/z 406/408/4120/412 (93.4/97.1/37.5/6.8) $[M+NH_4]^+$, 389/391/393/395 (34.2/35.2/14.0/2.5) $[M+H]^+$, 235/237/239 (81.6/60.5/12.4) $[(p\text{-}ClC_6H_4)_2CH]^+$, 139/141 (100.0/38.0) $[p\text{-}ClC_6H_4CO]^+$, 94 (8.9), 93 (21.5). HRMS (ESI) for $C_{21}H_{15}Cl_3O$ $[M+Na]^+$: Calc. 411.0086. Found 411.0089.

2-[2,2-Bis(4-chlorophenyl)ethyl]-2-(4-chlorophenyl)-thiozolidin-4-one E_{1A} (3)

A mixture of the adduct 1,3,3-tris(4-chlorophenyl)propan-1-one **P (2)**, (890 mg, 2.3 mmol), thioglycollic acid (280mg, 3.0 mmol) and ammonium carbonate (1160 mg, 12.1 mmol) in dry benzene (20 ml) was refluxed for 40h with stirring at 80°C on an oil bath, collecting the generated water in an azeotropic collector. The progress of the reaction was monitored by TLC at every 30 min. After the reaction was over, the reaction mixture was concentrated under reduced pressure, extracted with diethyl ether and washed with water until the solution became neutral. The ethereal solution was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The orange-coloured oily residue left was finally examined by TLC (silica gel 'G', pet.-ether (40-60°C)-diethyl ether, 7:3 v/v) which showed only one component, labelled as E_{1A}. The oily residuce was chromatographed over a silical gel column using pet ether (40-60°)-diethyl ether (3:7 v/v) as an eluent. Elution of the column furnished a light yellow-coloured solid which on crystallisation from benzene-acetone (9:1 v/v) afforded E_{1A} (3) as white crystalline globules, 615 mg. (58.6%). m.p. 170°C, R_f 0.85 (pet. ether (40-60°)-diethyl ether, 1:1 v/v).

Spectral data of E_{1A} (3)

IR (KBr pellet) : υ_{max} cm^{-1} : 3380 (NH), 1665 (-CONH), 1600, 1590 (phenyl), 1470 (S-CH_2), 1405 (C-H), 1250, 1080, 1010, 825.

^{1}H-NMR (acetone-d_6, 400 MHz, temp. 30°C) : δ_H 3.45 (1H, d, J=15.42Hz, H-5up), 3.56 (1H, d, J=15.42Hz, H-5dn), 8.04 (1H, brs, NH), 3.05 (1H, dd, J=14.80Hz, J=5.03Hz, H-1'up), 3.16 (1H, dd, J=14.80Hz, 7.78 Hz, H-1'dn), 4.33 (1H, dd, J=5.03Hz, J=7.78Hz, H-2'), 7.46 (2H, d, J=8.86Hz, H-Ar-2,6), 7.31 (2H, d, J=8.86Hz, H-Ar-3,5), 7.30 (2H, d, J=8.40Hz, H-Ar'-2,6),

7.20(2H,d,J=8.40Hz, H-Ar'-3,5), 7.36 (2H, d, J=8.55Hz, H-Ar"-2,6), 7.28 (2H, d, J=8.55Hz, H-Ar"-3,5).

^{13}C-NMR (100MHz, acetone-d_6, temp. 30°C) : δ_C 70.84 (C-2), 173.58 (C-4), 33.51 (C-5), 49.91 (C-1'), 47.89 (C-2'), 145.21 (C-Ar-1), 127.91 (C-Ar-2,6), 129.10 (C-Ar-3,5), 133.69[a] (C-Ar-4). 144.90[b] (C-Ar'-1), 130.52 (C-Ar'-2,6), 129.32 (C-Ar'-3,5), 132.55[a] (C-Ar'-4) 144.25[b] (C-Ar"-1), 130.26 (C-Ar"-2,6), 129.44 (C-Ar"-3,5), 132.40[b] (C-Ar"-4) [[a]Assignment may be reversed, [b]Assignment may be reversed].

DCI-MS (NH_3) : m/z 479/481/483/485 (21.0/22.7/10.0/4.4), $[M+NH_4]^+$, m/z 462/464/466/468 (89.6/100.0/44.8/8.8) [M+1], 238(8.2), 237(21.3), 236(11.7), 235(28.9), 228(6.8), 226 (10.3), 215 (7.9), 215 (7.9), 214 (23.1), 213(20.0), 212 (50.6) 165(12.4), 134(6.5), 117 (7.2). **HRMS (ESI)** for $C_{23}H_{18}Cl_3NOS$ $[M+H]^+$: Calculated 462.0253. Found 462.0264.

1,5-Bis(3,4-dimethoxyphenyl)pent-1,4-dien-3-one (4)

It was prepared following a literature procedure[123] by condensing acetone with 3,4-dimethoxybenzaldehyde (molar ratio, 1:2) in the presence of 2.5 equivalents of sodium hydroxide. A mixture of 3,4-dimethoxybenzaldeyde (5 gm, 0.0301 mol) dissolved in ethanol (20 ml) and acetone (0.873 gm, 0.0151 mol) was kept stirring on an ice bath and to this was added sodium hydroxide (1.51 gm, 0.038 mol, 10%) dropwise. A flocculent precipitate was formed during addition within 5 mintues. After complete addition, it was stirred further for 1 h, then filtered and the precipitate washed several times with cold water and finally with alcohol. The yellow solid mass thus obtained was crystallised from benzene to give **(4)** as yellow crystalline needles 3.720 gm (65%), m.p. 125 °C, R_f 0.67 (pet. ether-EtOAc, 8:2 v/v).

1,5-Bis(4-chlorophenyl)-1,5-bis(3,4-dimethoxyphenyl)pentan-3-one SFD (5)

To a suspension of 1,5-bis (3,4-dimethoxyphenyl) pent-1,4-dien-3-one (4) (1.5 g, 0.0042 mol) and anhydrous aluminium chloride (1.69 g, 0.0126mol) in chlorobenzene (10 ml), was added dry chlorobenzene (60 ml) slowly with stirring at room temperature. After complete addition, the reaction mixture was further stirred for 8 h and worked up as usual. The products on purification by column chromatography over silica gel using pet. ether (40-60°)-benzene (7.3 v/v) as eluent yielded **SFD (5)** as yellow semi solid mass, 2.13 g (70%), R_f 0.60 (pet. ether (40-60°)-benzene 8:2 v/v).

Spectral data of SFD (5)

IR (KBr pellet) : υ_{max} cm^{-1} 2928 (CH), 1711 (C=O), 1595, 1476 (phenyl), 1356, 1090, 1016, 759, 603.

^{1}H-NMR ($CDCl_3$, 300 MHz, temp. 27°C) : δ_H 4.43 (2H, dd, $J_{2up/4up,\ 2dn/4dn}$ = 13.20Hz, $J_{2up/4up,\ 1/5}$ = 6.60 Hz, H-2up/4up), 4.47 (2H, dd, $J_{2up/4up,\ 2dn/4dn}$ = 13.20Hz, $J_{2dn/4dn,\ 1/5}$ = 6.30 Hz, H-2dn/4dn), 4.99 (1H, dd, $J_{2up/4up,\ 1/5}$,=6.60 Hz, $J_{2dn/4dn,1/5}$=6.30 Hz, H-1/5), 3.13 (12H, s, 4 x OCH_3), 6.84-7.31 (14H, brm, H-Ar).

^{13}C-NMR ($CDCl_3$, 75 MHz, temp. 27°C) : δ_C 41.30 (C-2/C-4), 48.90 (C-1/ C-5), 44.50 (4 x OCH_3), 205.1 (C-3), 125.70-141.45 (4 x Ar - C).

FAB-Mass (JEOL SX 102/DA-6000) : m/z 545 (12.49), 543 (8.33), 541 (6.0), 529/531 (54.16/29.16), 495 (5.20), 493 (8.33), 491 (9.37), 391 (16.66), 392 (4.0), 293 (4.16), 291 (16.20), 289 (3.0), 279 (2.80), 277 (4.99), 253 (2.0), 251 (10.41), 249 (14.16), 239 (14.58), 237 (85.41), 235 (100.0), 203 (3.74), 201 (10.84), 199 (20.84), 178 (14.16), 167 (4.16), 165 (47.91), 154 (20.84), 151/149 (12.49/4.16), 138 (7.91), 137 (14.16), 136 (16.66), 127/125 (4.16/8.33), 107 (6.24).

2,2-Di[2-(4-chlorophenyl)-2-(3,4-dimethoxyphenyl)ethyl] thiazolidin-4-one SFD_{1C} (6)

To a solution of the adduct **SFD (5)** (900mg, 1.557 mmol) in dry benzene (25 ml), thioglycollic acid (186 mg, 2.024 mmol) and ammonium carbonate (785 mg, 8.17 mmol) were added. The reaction mixture was refluxed for 40 h with stirring, collecting the generated water in azeotropic collector and then worked up as usual. The products on purification over a silica gel column (pet. ether (40-60°) - diethyl ether, 7:3 v/v as eluent) and crystallization (benzene-acetone, 9:1 v/v) yielded **SFD_{1C} (6)** as white crystalline globules, 557 mg (55%), m.p 204°C, R_f 0.62 (benzene - EtOAc, 7:3 v/v).

Spectral data of SFD_{1C} (6)

IR (KBr pellet) : υ_{max} cm^{-1} 3400 (NH), 2912 (C-H), 1674 (-CONH), 1594 (phenyl), 1485 (-S-CH_2), 1410 (C-N), 1366, 1239, 1208, 1092, 1012, 818, 780.

^{1}H-NMR ($CDCl_3$, 300 MHz, temp. 25°C) : δ_H 2.35 (2H, dd, $J_{1'up/1"up,\ 1'dn/1"dn}$ = 14.70Hz, $J_{1'up/1"up,\ 2/2"}$ = 4.80Hz, H-1'/1"up), 2.58 (2H, dd, $J_{1'up/1"up,\ 1'dn/1"dn}$ = 14.70Hz, $J_{1'dn/1"dn,\ 2'/2"}$ = 6.90Hz, H-1'dn/1"dn), 3.43 (12H, s, 4 x OCH_3), 4.22 (2H, s, H-5), 4.7(1H, s, H-2'/2"), 7.70 (1H, s, NH), 7.04-7.37 (14H, brm, H-Ar).

^{13}C-NMR ($CDCl_3$, 75MHz, temp. 30°C) : δ_C 33.50 (C-5), 42.20 (C-2'/C-2"), 46.34 (4 x OCH_3), 48.70 (C-1'/C-1"), 70.40 (C-2), 172.1 (C-4), 125.3-143.0 (4xAr-C).

EI-MS : m/z 528 (85.60), 526(50.75), 366(10.0), 364(3.03), 352(59.09), 332(3.03), 322(1.51), 292 (0.75), 290 (9.85), 276 (3.79), 274 (25.0), 260 (1.52), 238 (12.88), 236 (100.0), 234 (12.12), 203 (6.06), 165 (55.30), 92 (2.27), 86(6.06).

2,2-Di[2-(4-chlorophenyl)-2-(3,4-dimethoxyphenyl)ethyl]-5-(methyl)thiazolidin-4-one SFD_{1E} (7)

To a solution of the adduct **SFD** (5) (900 mg, 1.557 mmol) in dry benzene (25 ml), 2-mercaptopropionic acid (214 mg, 2.024 mmol) and ammonium carbonate (785mg, 8.17 mmol) were added. The reaction mixture was refluxed for 45 h with stirring and collecting the generated water in an azeotropic collector and then worked up as usual. The products on purification over a silica gel column (pet. ether (40-60°)-diethyl ether, 7:3 v/v as eluent) and crystallization (benzene-acetone, 8:2 v/v) afforded **SFD_{1E}** (7) as white crystalline globules, 590 mg (57%), m.p 208°C, R_f 0.73 (benzene-EtOAc, 7:3 v/v).

Spectral data of SFD_{1E} (7)

IR (KBr pellet) : υ_{max} cm^{-1} 3453 (NH), 2900 (CH), 1681 (CONH), 1593, 1485 (phenyl), 1435 (S-CH-CH_3) 1371, 1242, 1197, 1092, 1012, 810.

^{1}H-NMR ($CDCl_3$, 300 MHz, temp. 25°C) : δH 2.29 (2H, dd, $J_{1'up/1"up,\ 1'dn/1"dn}$ = 14.70Hz, $J_{1'up/1"up,\ 2'/2"}$ = 4.50Hz, H-1'up/1"up), 2.46 (2H, dd, $J_{1'up/1"up,1'dn/1"dn}$ = 14.70Hz, $J_{1'dn/1"dn,\ 2'/2"}$ = 6.30Hz, H-1'dn/1"dn), 4.72 (1H, dd, $J_{1'up/1"up,2'/2"}$=4.50 Hz, $J_{1'dn/1"dn,2"/2"}$=6.30 Hz, H-2'/2"), 4.12-4.15 (12H, s, 4 x OCH_3), 3.83 (1H, q, J=6.90Hz, H-5), 1.54 (3H, d, J = 6.90Hz, H-5-CH_3), 6.98-7.29 (14H, brm, H-Ar).

EI-MS : m/z 616 (9.84), 614 (3.78), 582 (1.52), 580 (2.27), 491 (2.27), 380 (3.79), 378 (10.60), 366 (55.30), 364 (46.21), 336 (2.65), 290 (2.27), 275 (32.58), 273 (22.72), 249 (2.27), 239 (17.42), 238 (18.18), 237 (68.18), 236 (23.48), 235 (100.0), 201 (1.52), 199 (0.75), 165 (9.84), 106 (9.84), 86 (2.27).

1,5-Bis(4-chlorophenyl)pent-1,4-dien-3-one(8)

It was prepared as described above by condensing acetone with *p*-chlorobenzaldehyde (molar ratio, 1:2) in the presence of 2.5 equivalents of sodium hydroxide. To a solution of *p*-chlorobenzaldehyde (6.84 gm, 0.049 mol) dissolved in ethanol (20 ml) was added acetone (1.42 gm, 0.0244 mol) dropwise and the solution was kept on an ice bath in a 500 ml flask. To this was added sodium hydroxide solution (4.8 gm, 0.123 mol,10%) slowly and was kept stirring for 2.5 h. The yellow precipitate formed was filtered and washed successively with water and finally with alcohol and then crystallized from benzene to give **(8)** as yellow crystalline needles, 6.30 gm (79%), m.p. 176 °C, R_f 0.72 (pet. ether-EtOAc, 8:2 v/v).

^{1}H-NMR (acetone-d_6 400MHz,) : δ_H 7.28 (2 x 1H, d, J=16.0, H-2), 7.70 (2 x 1H, d, J=16.0, H-3), 7.73 (2 x 2H, d, J=8.50, 2xAr-2,6), 7.45 (2 x 2H, d, J=8.50, Ar-3,5).

1,1,5,5-Tetra(4-chlorophenyl)pentan-3-one ClFD (9)

To a suspension of 1,5-bis(4-chlorophenyl) pent-1,4-dien-3-one **(8)** (2g, 0.0066 mol) and anhydrous aluminium chloride (2.692 gm, 0.0199 mol) in chlorobenzene (10 ml) was added chlorobenzene (90 ml) slowly with stirring at room temperature. After complete addition, the reaction mixture was stirred for 10 h. and worked up as usual. The product on column chromatography over silica gel using pet. ether (40-60°)-benzene, 7:3 v/v as an eluent afforded **ClFD (9)** as light yellow-coloured semi solid mass, 3.35 g (76%), R_f 0.62 (pet. ether (40-60°)-benzene, 8:2 v/v).

Spectral data of ClFD (9)

IR (KBr pellet) : $\upsilon_{max\ cm^{-1}}$ 2924 (CH), 1710 (C=O), 1592, 1572, 1490 (Phenyl), 1408, 1095, 1059, 1008, 819, 747 (C-Cl), 686.

^{1}H-NMR ($CDCl_3$, 300 MHz, temp. 20°C) : δ_H 3.02 (2H, dd, $J_{2up/4up,2dn/4dn}$ = 17.10Hz, $J_{2up,/4up,\ 1/5}$ = 9.90 Hz, H-2up/4up), 3.14 (2H, dd, $J_{2up/4up,\ 2dn/4dn}$ = 17.10Hz, $J_{2dn/4dn,\ 1/5}$ = 4.80 Hz, H-2dn/4dn), 4.49 (2H, dd, $J_{2up/4up,1/5}$ = 9.90 Hz, $J_{2dn/4dn,1/5}$ = 4.80Hz, H-1/5), 6.95-7.36 (16H, brm, H-Ar).

^{13}C-NMR (DMSO, 75 MHz, temp. 27°C) : δ_C 43.98 (C-2/C-4), 47.21 (C-1/ C-5), 205.67 (C-3), 128.29-142.83 (4 x Ar-C).

FAB-Mass (Argon/Xenon, 6KV, 10mA, as the FAB gas) : m/z 535 (2.50), 533 (2.60), 531 (5.72), 529 (9.80), 527 (6.77), 497 (1.00), 495 (1.60), 493 (2.00), 491 (2.08), 295 (1.04), 293 (2.29), 291 (4.16), 281 (1.0), 279 (3.8), 277 (4.0), 253 (2.08), 252 (1.60), 251 (2.40), 250 (1.80), 249 (3.70), 248 (2.0), 239 (11.45), 237 (64.50), 235 (100.0), 201 (10.41), 1`99 (12.49), 180 (2.0), 178 (8.0), 167 (10.41), 165 (29.16), 151 (4.4), 149 (41.66), 139 (6.0), 137 (8.0), 113 (12.49), 111 (9.37).

2,2-Di[2,2-bis(4-chlorophenyl)ethyl]-5-(methyl)thiazolidin-4-one $ClFD_{1C}$ (10)

A mixture of 1,1,5,5-tetra(4-chlorophenyl)pentan-3-one (9) (950 mg, 1.80 mmol), 2-mercaptopropionic acid (248 mg, 2.34 mmol) and ammonium carbonate (910 mg, 9.48 mmol) in dry benzene (50 ml) was refluxed for 45 h with stirring at 80°C on an oil bath using an azeotropic collector. The progress of the reaction was monitored by TLC at every 30 min. The reaction mixture was then concentrated under reduced pressure, extracted with diethyl ether and washed with water until the solution was neutral. The ethereal solution was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The orange-coloured oily residue left was purified by passing over a silica gel column (using pet. ether (40-60°)-diethyl ether, 7:3 v/v as an eluent) and then crystallized (benzene-acetone, 8:2 v/v) to give **$ClFD_{1C}$ (10)** as white

crystalline globules, 620 mg (56.00%), m.p 168°C, R_f 0.65 (benzene EtOAc, 7:3 v/v).

Spectral data of $ClFD_{1C}$ (10)

IR (KBr pellete) : υ_{max} cm^{-1} 3425 (NH), 2909 (CH), 1680 (-CONH), 1591, 1484 (phenyl), 1450 (S-CH-), 1435 (C-N), 1357, 1243, 1193, 1091, 1010, 949, 869, 813, 777.

^{1}H-NMR ($CDCl_3$, 300 MHz, temp. 25°C) : δ_H 1.56 (1H, s, 5-CH_3), 2.30 (2H, dd, $J_{1'up/1"up,\ 1'dn/1"dn}$ = 16.20Hz, $J_{1'up/1"up,\ 2'/2"}$ = 4.20Hz, H-1'up/1"up), 2.42 (2H, dd, $J_{1'up/1"up,\ 1'dn/1"dn}$ = 16.20Hz, $J_{1'dn/1"dn,\ 2'/2"}$ = 7.20Hz, H-1'dn/ 1"dn), 4.16 (1H, dd $J_{1'up/1"up,\ 2'/2"}$ = 4.20Hz, $J_{1'dn/1"dn\ 2'/2"}$ = 7.20Hz, H-2'/2"), 3.81 (1H, q, J=6.60Hz, H-5), 7.29 (1H, s, NH), 6.98-7.22 (16H, brm, H-Ar).

^{13}C-NMR ($CDCl_3$, 75 MHz, temp. 30°C) : δc 19.58 (5-CH_3), 42.21 (C-5), 49.50 (C-1'/C-1"), 46.62 (C-2'/C-2"), 68.32 (C-2), 175.29 (C-4), 125.80-142.97 (4 x Ar-C).

FAB-MASS (Agron/Xenon (6KV, 10mA, as the FAB gas) : m/z 622(2.20), 620 (7.29), 619 (8.33), 618 (22.92), 617 (18.75), 616 (43.74), 615 (17.70), 614 (32.29), 613 (4.0), 392(2.0), 391 (9.37), 368 (4.0), 366 (12.50), 364 (14.58), 239 (10.41), 238 (8.0), 237 (62.49), 236 (14.0), 235 (100.0), 201 (6.66), 200 (4.0), 199 (8.33), 167 (2.0), 166 (7.92), 165 (25.0), 155 (8.0), 154 (37.50), 149 (12.49), 139 (4.0), 138 (10.0), 137 (17.70), 136 (27.08), 107 (6.0).

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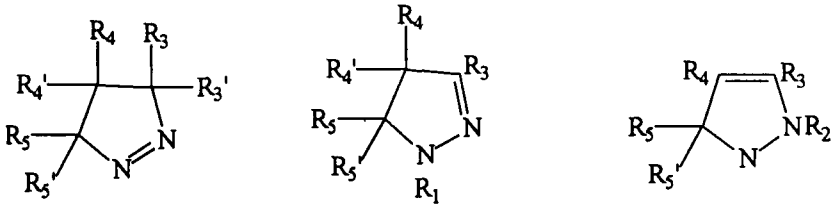
Chapter - 2

3,5-Disubstituted-2-Pyrazolinyl-Thiocarboxamides

Theoretical

THEORETICAL

Pyrazolines belong to an important class of biologically active five membered heterocyclic compounds containing two nitrogen atoms at 1,2 positions and one double bond in the ring. There are three isomeric forms of pyrazolines as Δ^1–**(I)**, Δ^2–**(II)**, Δ^3–**(III)** depending upon the positions of double bond.



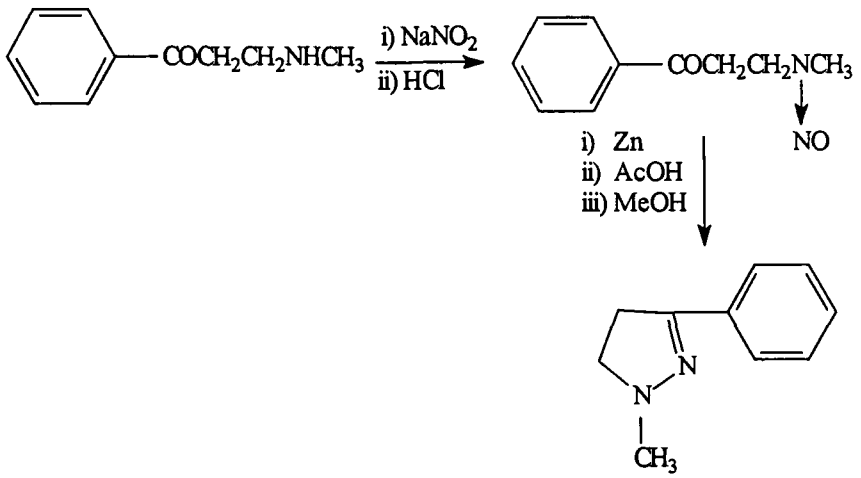
(I) **(II)** **(III)**

$R_1 = R_2 = R_3 = R_3' = R_4 = R_4' = R_5 = R_5' =$ H or alkyl or aryl.

Pyrazoline derivatives have been studied extensively because of their ready accessibility, diverse chemical reactivity, broad spectrum of biological activity and variety of industrial applications[1-5]. A study on pyrazolines still is an intriguing subject because of their varied bioactive nature. Pyrazoline derivatives are known to possess various biological activities, such as antibacterial[6-15], antifungal[16-26], insecticidal[27-39], pesticidal[40-42], herbicidal[43-46], acaricidal[29], antiinflammatory[47-58], analgesic[48,59], arthropodicidal[60-64], antiallergic[65], anti-histaminic[66], diuretic[67], mildewicidal[68], antiviral[69], antitumor and anti-HIV activity[70-71], anti-depressant[72-73], hypoglycemic activity[74-75]. It has been reported that introduction of 1-acetyl group at 1-position enhances the molluscidal activity[76-79] as well as increases the stability of 2-pyrazolines and substitution at 3-position in indole nucleus with different moieties markedly affects the hypotensive activity[80-82]. A number of pyrazoline derivatives has also been found to exhibit highly potent as

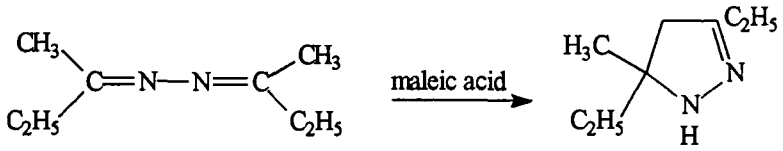
cerebroprotective action[83-85]. Pyrazoline derivatives substituted at 1-position are reported to be cardiovascular agents[86-87]. Also, 1-aryl-2-pyrazolines are found to be useful as antioxidant composition in polymer[88] and in the treatment of cerebral edema[89]. Pyrazoline nucleus attached to indole ring systems have been shown to exhibit monoamine oxidase inhibitor activity[90]. Several haloanilido pyrazolines are used in textile and cinematographic film industry.[91]

Different methods are reported in literature for the preparation of pyrazoline derivatives. Mannich and Heilner[93] have prepared pyrazoline derivative **(IV)** by the cyclization of β-hydrazino carbonyl in acetic acid and methanol in presence of Zn.



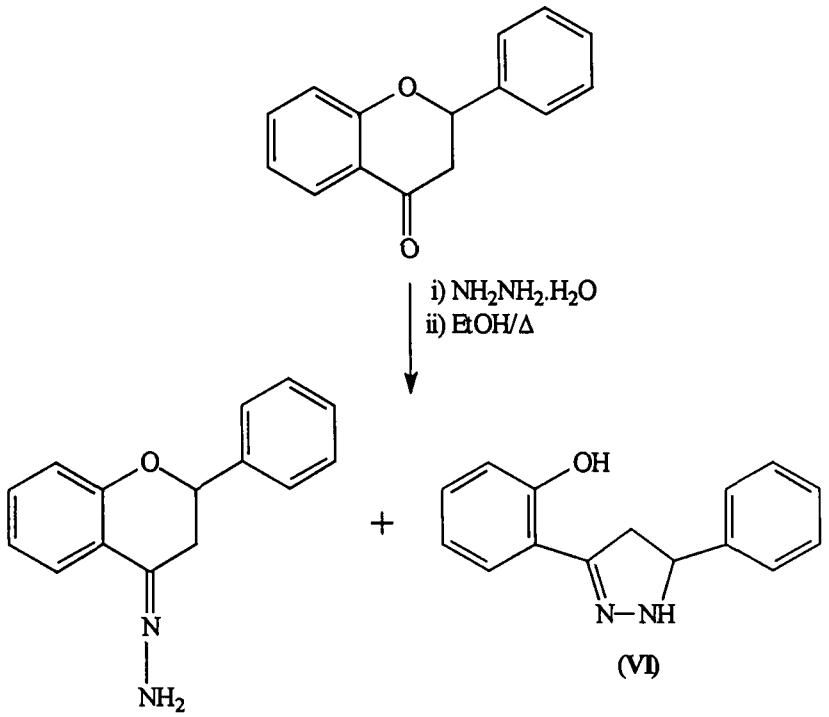
(IV)

Curtius *et al.*[94-96] have reported the synthesis of pyrazoline derivative **(V)** by the cyclization of azine of methyl ketone with maleic acid.



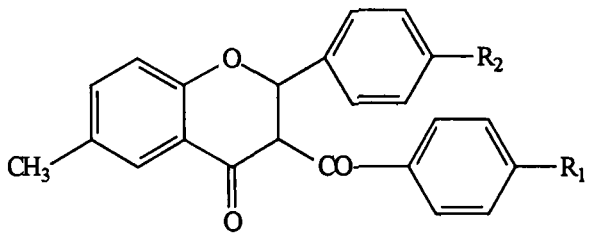
(V)

F. Kallay *et al.*[97] have synthesized 3-(*o*-hydroxyphenyl)-5-phenylpyrazoline **(VI)** by heating flavanone with hydrazine hydrate in ethanol.

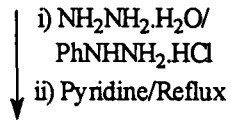


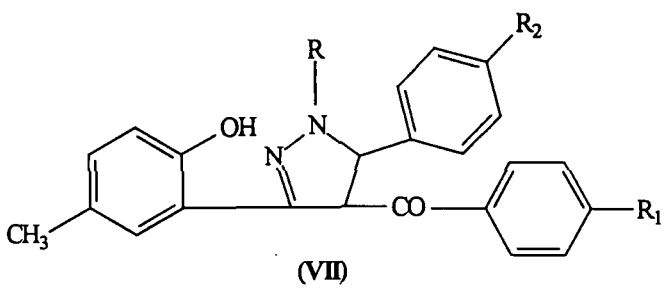
(VI)

Some new 4-aroyl-substituted pyrazolines[98] **(VII)** have been synthesized by the condensation of hydrazine hydrate or phenylhydrazine hydrochloride with 3-aroylflavanones in pyridine.



a $R_1 = R_2 = H$
b $R_1 = H, R_2 = OCH_3$
c $R_1 = OCH_3, R_2 = H$

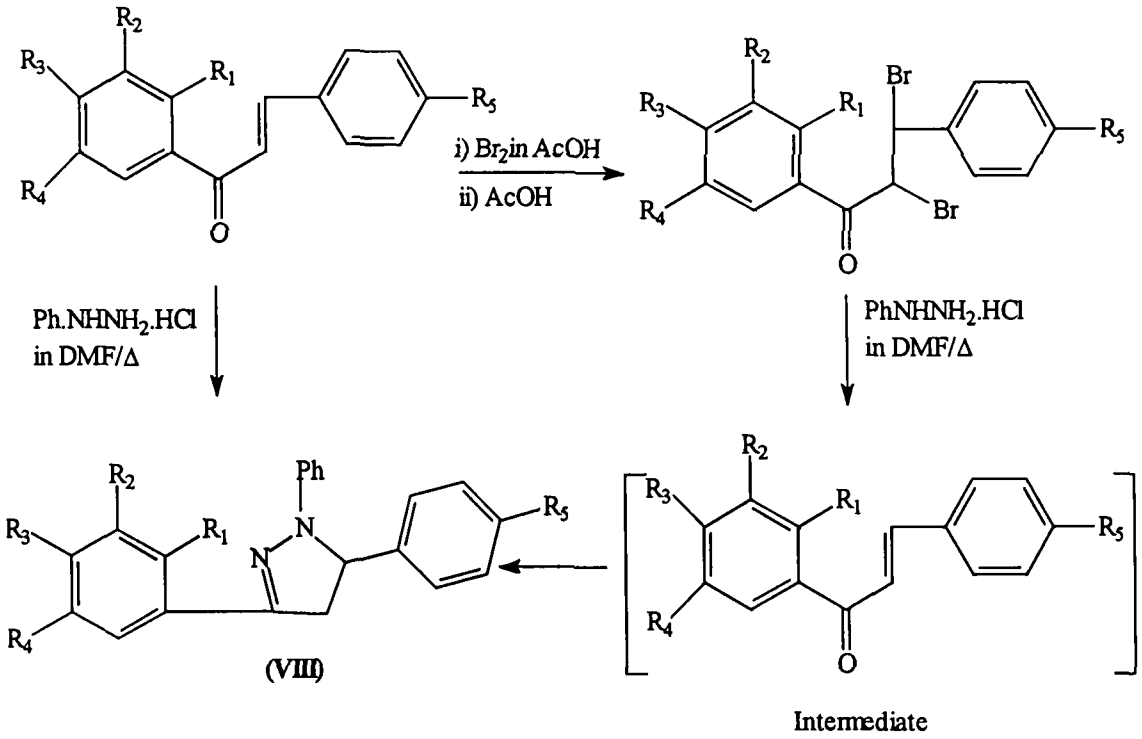




(VII)

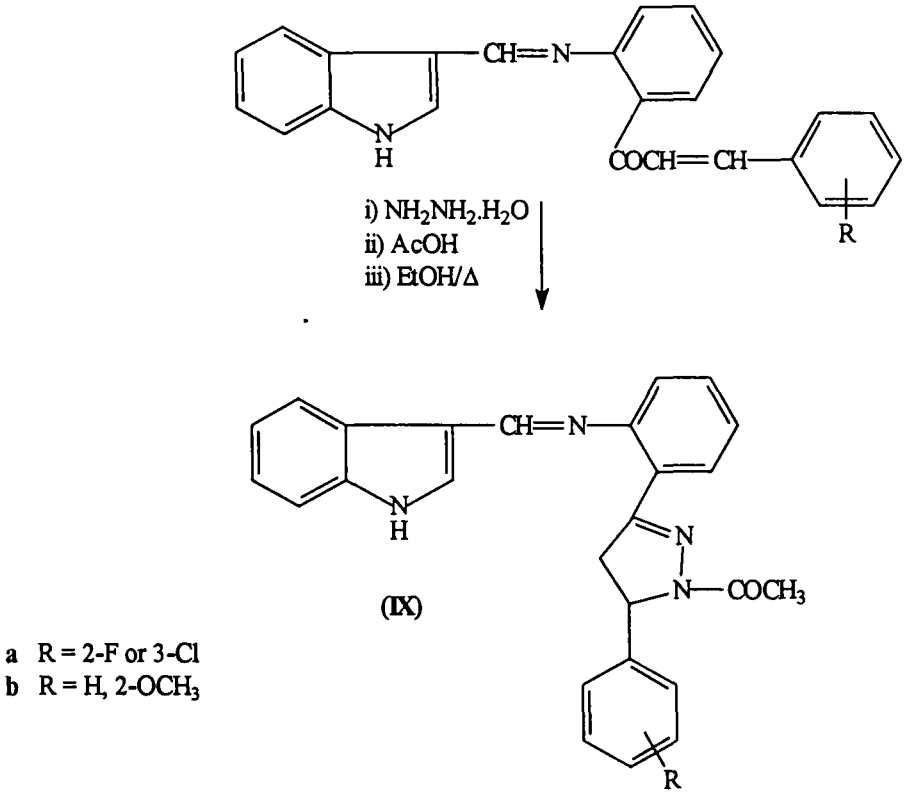
a $R_1 = R_2 = R = H$
b $R_1 = R = H, R_2 = OCH_3$
c $R_1 = OCH_3, R_2 = R = H$
d $R_1 = R_2 = H, R = Ph$
e $R_1 = H, R_2 = OCH_3, R = Ph$
f $R_1 = OCH_3, R_2 = H, R = Ph$

M.G. Joshi *et al.*[99] have synthesized 3,5-diaryl-1-phenyl pyrazolines (**VIII**) from chalcones or α,β-dibromochalcones by reacting with phenyl hydrazine hydrochloride in DMF.



	R_1	R_2	R_3	R_4	R_5
a	OH	H	H	CH_3	H
b	OH	H	H	CH_3	OCH_3
c	OH	Br	H	CH_3	H
d	OH	Br	H	CH_3	OCH_3
e	OH	H	H	H	H
f	OH	H	H	H	OCH_3
g	OH	H	CH_3	H	OCH_3
h	OH	H	CH_3	H	OCH_3
i	H	H	H	H	H
j	H	H	H	H	OCH_3

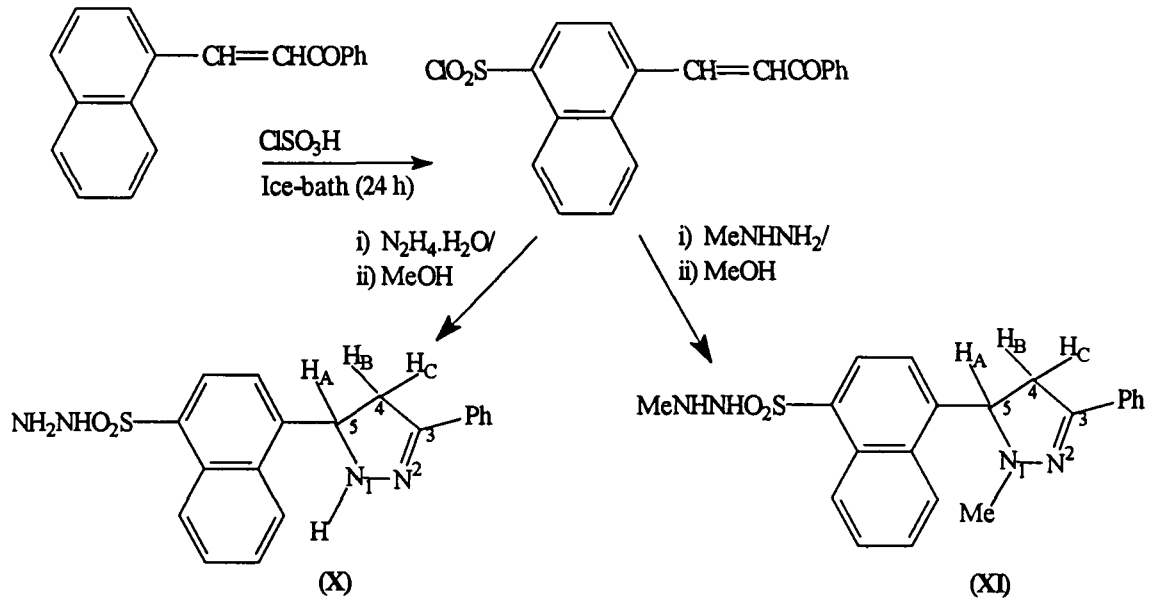
Kirpa Shanker and co-workers[81] have synthesized 1-acetyl-5-aryl-3-[*o*-(indol-3-yl-methyleneamino) phenyl]-2-pyrazolines (**IX**) by the cyclisation of substituted-2'-(indole-3-yl-methyleneamino)chalcones with hdyrazine hydrate in presence of glacial acetic acid.



(IX)

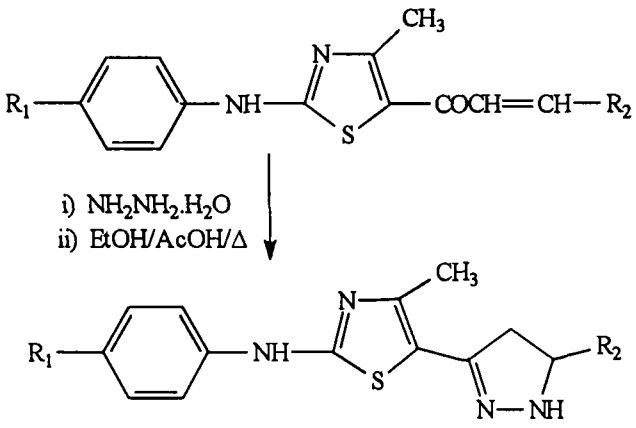
a R = 2-F or 3-Cl
b R = H, 2-OCH_3

R.J. Cremlyn *et al.*[100] prepared 3-phenyl-5-(4-*N*-methylhydrazino-sulfonyl-α-naphthyl)pyrazoline (**X**) and 3-phenyl-5-(4'-hydrazinosulfonyl-α-naphtyl) pyrazoline (**XI**) from 4-chlorosulphonyl-α-naphthyl chalcone by reaction with hydrazine hydrate and *N*-methyl hydrazine in methanol at room temperature.



(X) (XI)

Thiazolyl-pyrazoline derivatives[101] **(XII)** were prepared by the reaction of 2-arylamino-5-(3'-aryl/heteroaryl-acrylo)-4-methylthiazoles with hydrazine hydrate in ethanol in presence of acetic acid.

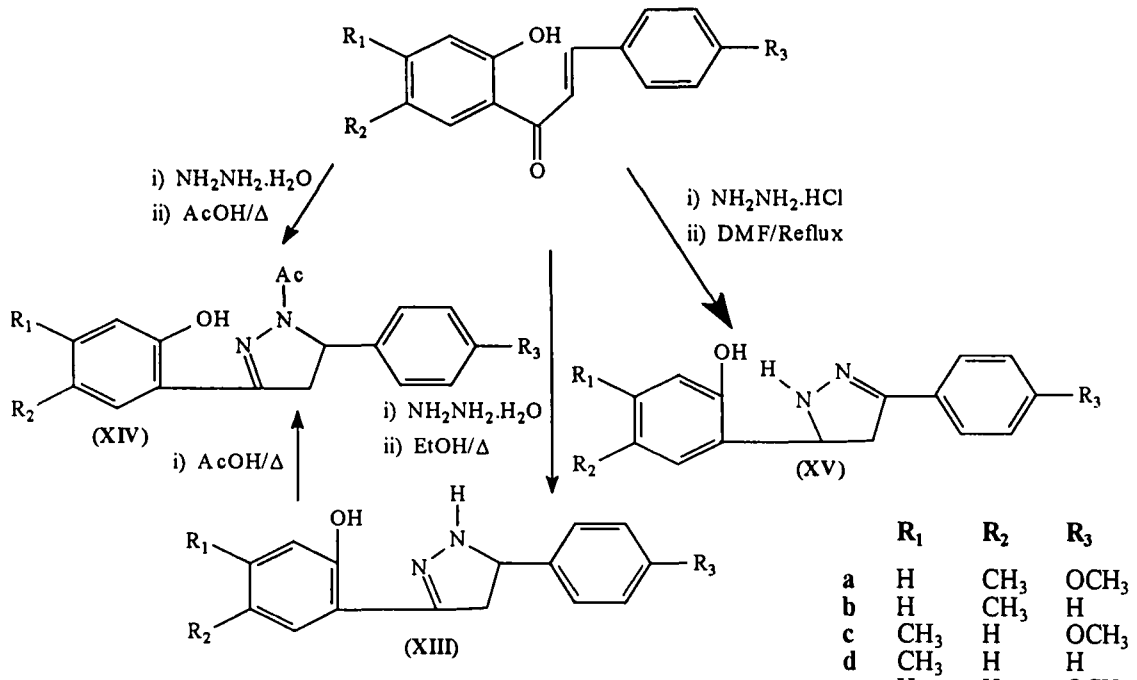


(XII)

R_1 = H or Br or Cl or Me or OMe or OEt

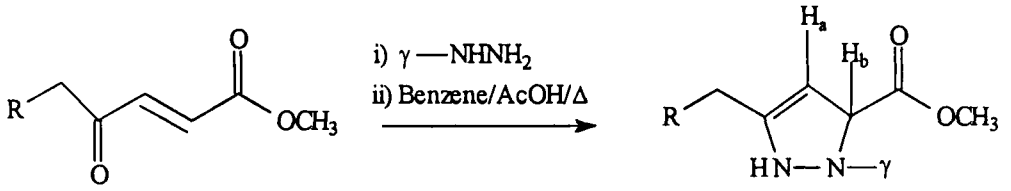
R_2 = Substituted phenyl or 2-Furyl or 2-Pyridyl or 2-Thienyl

V.G. Thakare *et al.*[102] have synthesized 5-aryl-3-(2-hydroxyphenyl)-Δ^2-pyrazolines **(XIII)** by heating 2'-hydroxy chalcones with hydrazine hydrate in ethanol while in acetic acid the corresponding 5-aryl-1-acetyl-3-(2-hydroxyphenyl)-Δ^2-pyrazolines **(XIV)** were obtained. However, 2'-hydroxychalcones react with hydrazine hydrochloride in DMF to give the isomeric 3-aryl-5-(2-hydroxyphenyl)-Δ^2-pyrazolines **(XV)**.



	R_1	R_2	R_3
a	H	CH_3	OCH_3
b	H	CH_3	H
c	CH_3	H	OCH_3
d	CH_3	H	H
e	H	H	OCH_3
f	H	H	H

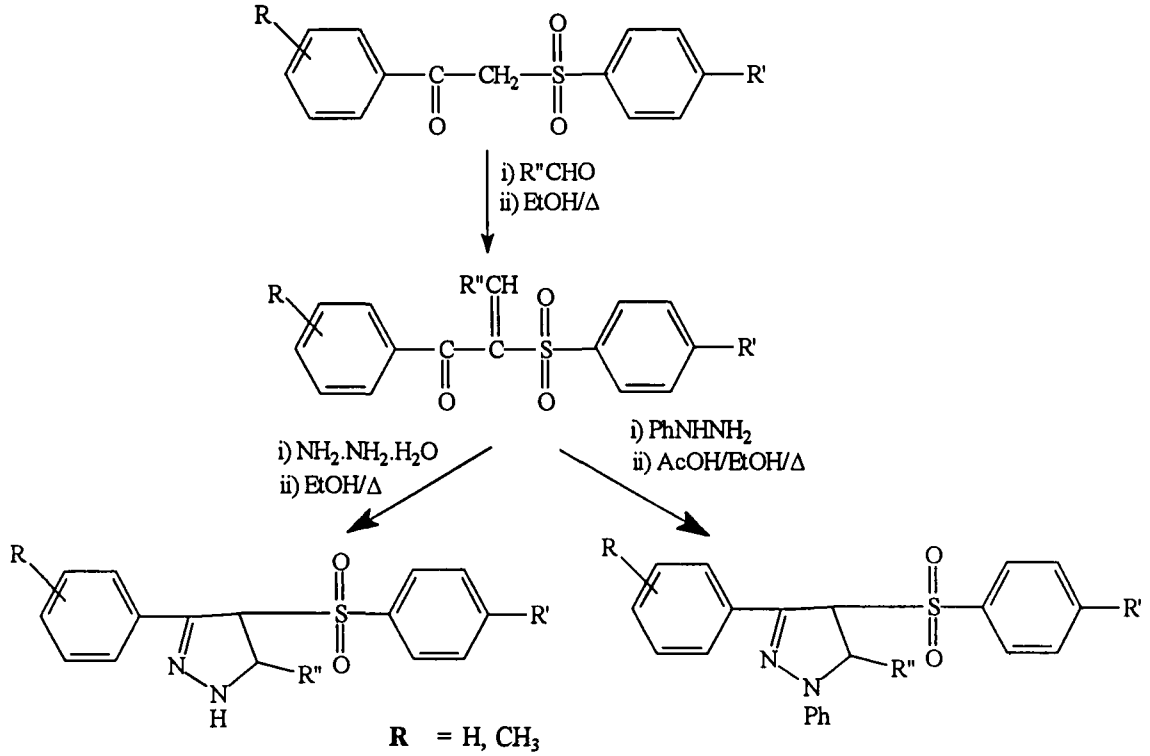
M. Ahmad and co-workers[103-104] have prepared pyrazoline derivatives **(XVI)** by heating methyl 4-oxooctadec-2(*E*)-enoates with phenyl hydrazine in benzene and acetic acid, which were screened for their antibacterial and antifungal potential.



R = $CH_3(CH_2)_{12}$,
γ = H, Ph, CH_3Ph

(XVI)

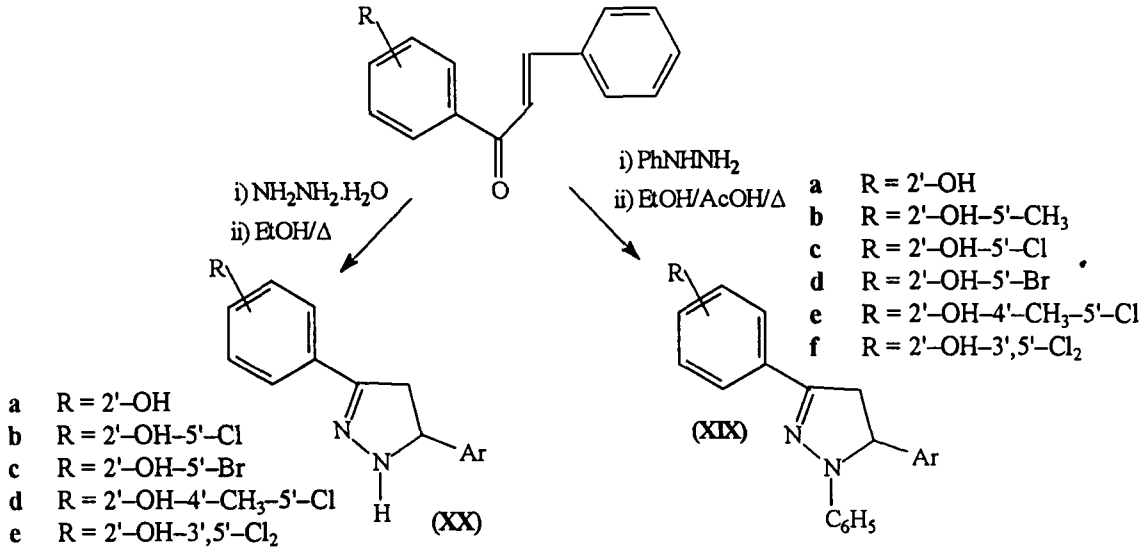
3-aryl-5-aryl/heteroaryl-4-arylsulphonyl pyrazolines **(XVII)** and 3-aryl-5-aryl/heteroaryl-4-aryl sulphonyl-1-phenyl pyrazolines **(XVIII)** have been synthesized by the condensation of chalcones with hydrazine hydrate and phenyl hydrazine in ethanol and these compounds have been tested for their different biological activities.[105]



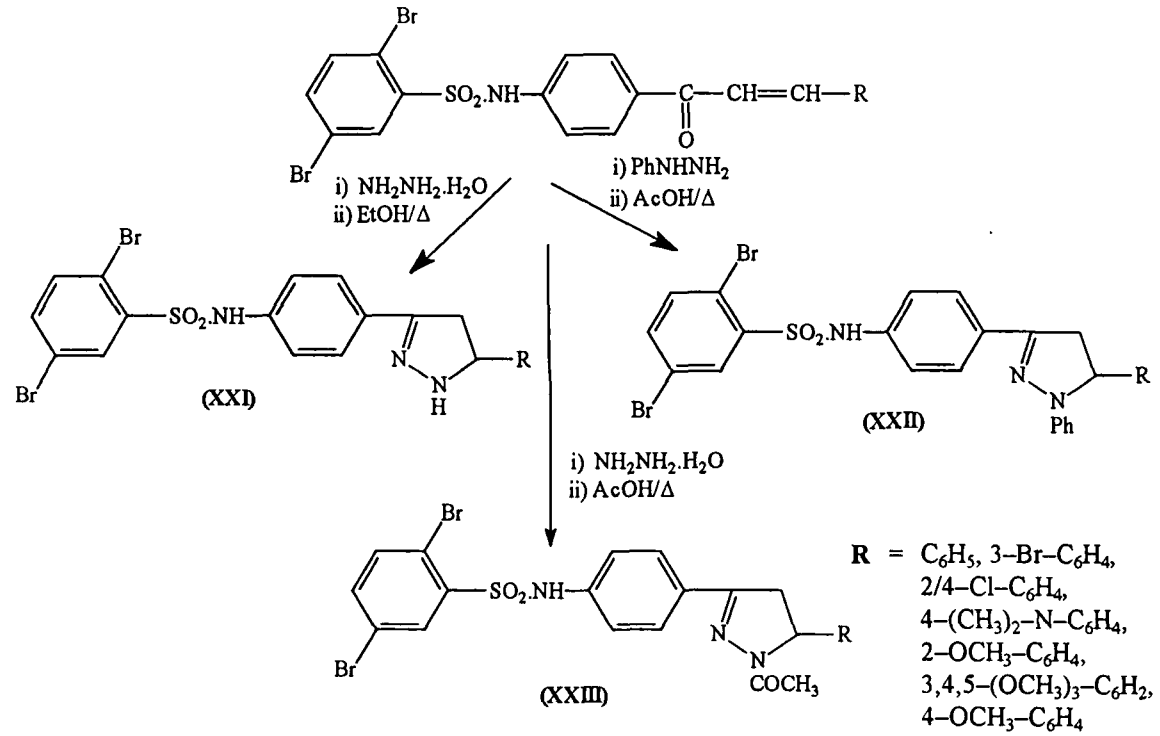
R = H, CH_3
R' = H, CH_3 and Cl
R" = Substituted phenyl and heteroaryl

(XVII) **(XVIII)**

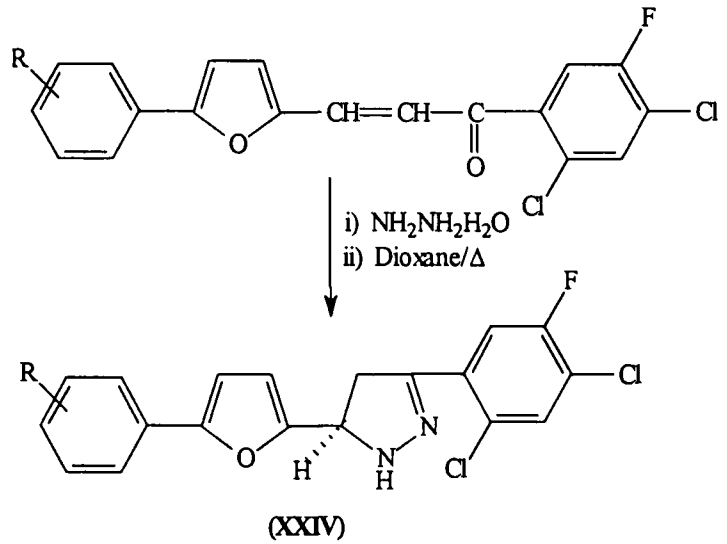
A number of pyrazoline derivatives[14,15,77,79,87,106-111] **(XIX, XX)** have been prepared from different chalcones using hydrazine hydrate or phenyl hydrazine and acetic acid. Some of these compounds showed potential biocidal activities.



A.R. Parikh and co-workers[112] have synthesized different pyrazoline derivatives **(XXI-XXIII)** by heating chalcones and hydrazine hydrate or phenyl hydrazine in ethanol.



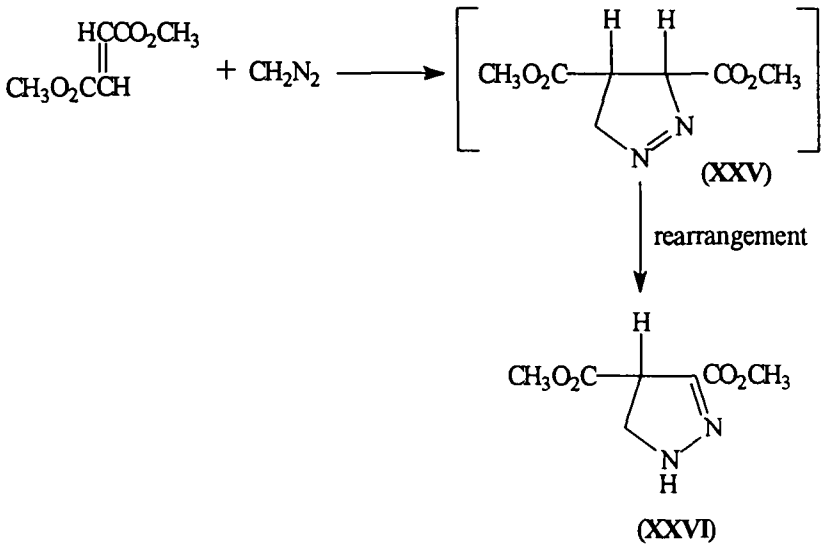
B.S. Holla *et al.*[8] have synthesized aryl furyl pyrazolines (**XXIV**) by heating arylfuryl propenones with hydrazine hydrate in dioxane and were tested for antibacterial activity.



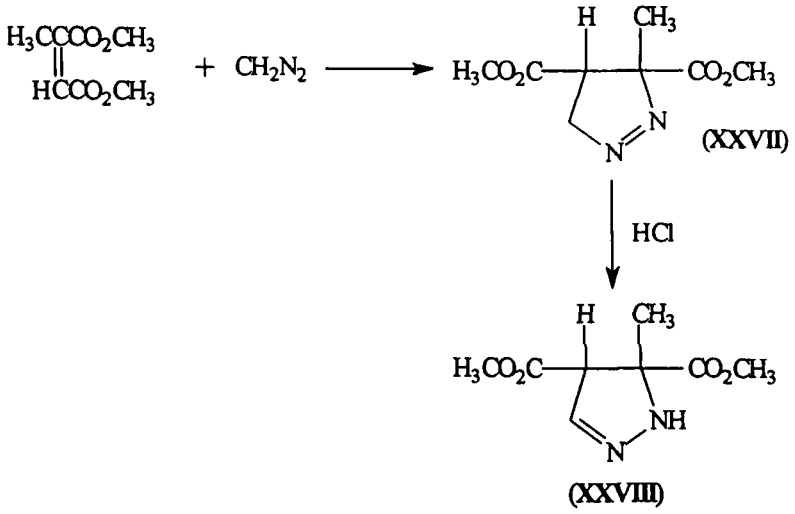
(XXIV)

	R
a	*p*-NO_2
b	*p*-Br
c	*p*-Cl
d	*m*-NO_2
e	*o*-NO_2

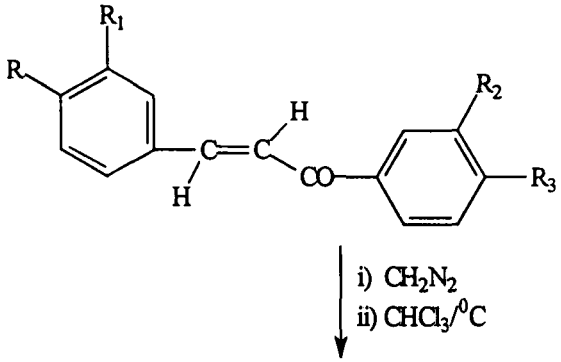
V. Auwers *et al.*[113] have synthesized pyrazoline derivatives (**XXV-XXVIII**) from α,β unsaturated esters and diazomethane.



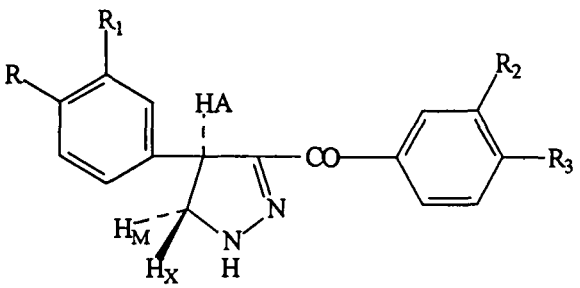
(XXVI)



CH.B. Rao *et al.*[114] have prepared 3-aroyl-4-aryl-Δ^2-pyrazolines (**XXIX**) through cycloaddition of diazomethane with chalcones. These compounds exhibit mild local anaesthetic, CNS depressant, and anticonvulsant activities.

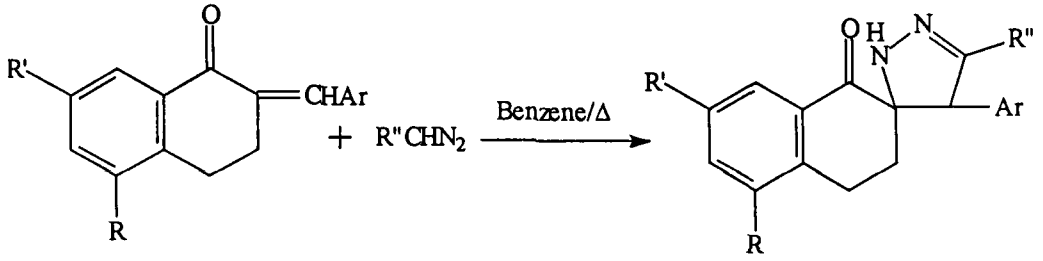


	R	R_1	R_2	R_3
a	H	H	H	H
b	H	H	H	OCH_3
c	H	OCH_3	H	H
d	H	NO_2	H	H
e	H	H	NO_2	H
f	NMe_2	H	H	OCH_3
g	NMe_2	H	H	H
h	OCH_3	H	H	H
i	NO_2	H	H	H
j	OCH_3	H	H	OCH_3
k	NO_2	H	H	OCH_3
l	$-OCH_2O-$	$-OCH_2O-$	H	H
m	H	H	H	NO_2



(XXIX)

A.K. Fateen *et al.*[115] have synthesized Δ^1-spiropyrazoline derivatives (**XXX**) by heating 2-arylidene-tetralones with diazomethane or diazoethane in benzene.

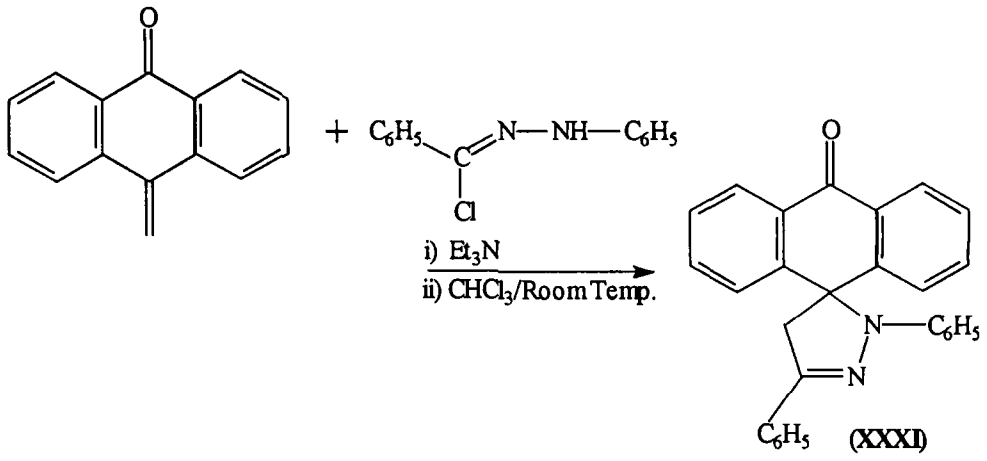


	R	R'	Ar
a	H	CH_3	Ph
b	H	CH_3	*p*-$MeOC_6H_4$
c	H	CH_3	PhCH=CH
d	H	CH_3	*p*-$NO_2C_6H_4$
e	H	CH_3	2-furyl[1]
f	CH_3	CH_3	Ph
g	CH_3	CH_3	PhCH=CH
h	CH_3	CH_3	*p*-$MeOC_6H_4$
i	CH_3	CH_3	*p*-$NO_2C_6H_4$
j	CH_3	CH_3	2-furyl[2]
k	H	Ph	Ph
l	H	Ph	*p*-$MeOC_6H_4$
m	H	OMe	Ph

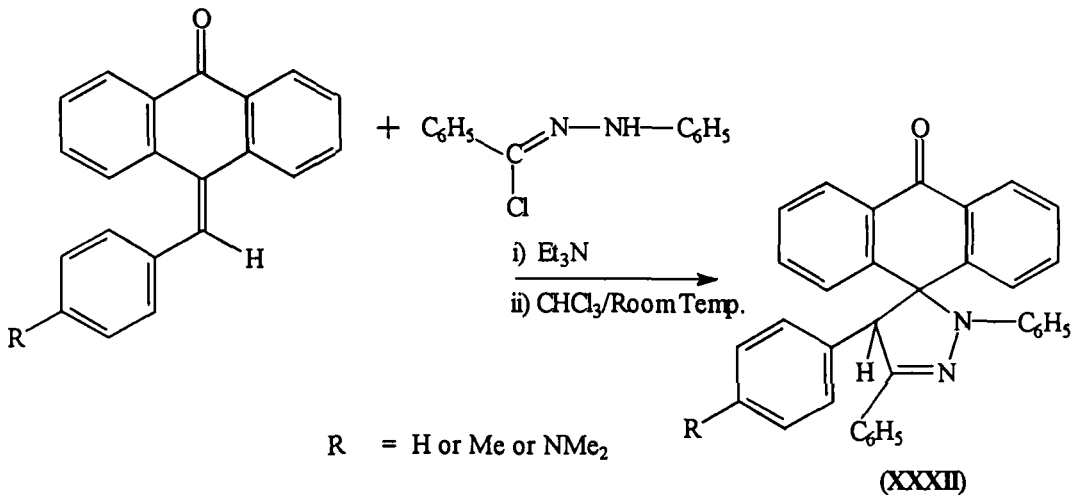
(XXX)

	R	R'	R"	Ar
a	H	CH_3	H	Ph
b	H	CH_3	CH_3	*p*-$MeOC_6H_4$
c	H	CH_3	CH_3	PhCH=CH
d	H	CH_3	CH_3	2–Furyl
e	CH_3	CH_3	H	Ph
f	CH_3	CH_3	H	PhCH=CH
g	CH_3	CH_3	H	*p*-$MeOC_6H_4$
h	CH_3	CH_3	CH_3	2-Furyl
i	H	Ph	CH_3	Ph
j	H	Ph	H	*p*-$MeOC_6H_4$
k	CH_3	CH_3	CH_3	PhCH=CH
l	CH_3	CH_3	CH_3	*p*-$MeOC_6H_4$
m	H	CH_3	CH_3	Ph
n	CH_3	CH_3	CH_3	Ph

Recently, R. Raghunathan and co-workers[116-117] have prepared a series of novel spiropyrazolines [5.9[1]] anthrones (**XXXI, XXXII**) by regioselective 1,3-dipolar cycloaddition of diphenylnitrilimine with 9-methyleneanthrone or 9-arylideneanthrone in chloroform.

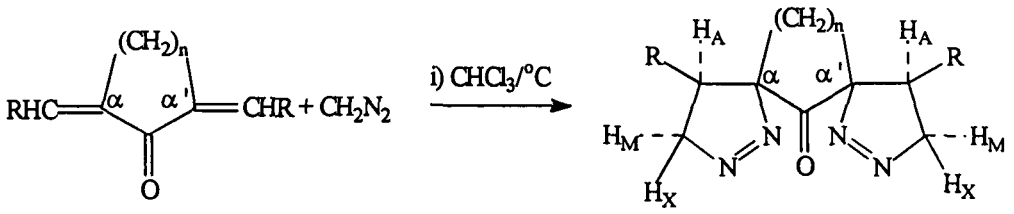


(XXXI)



(XXXII)

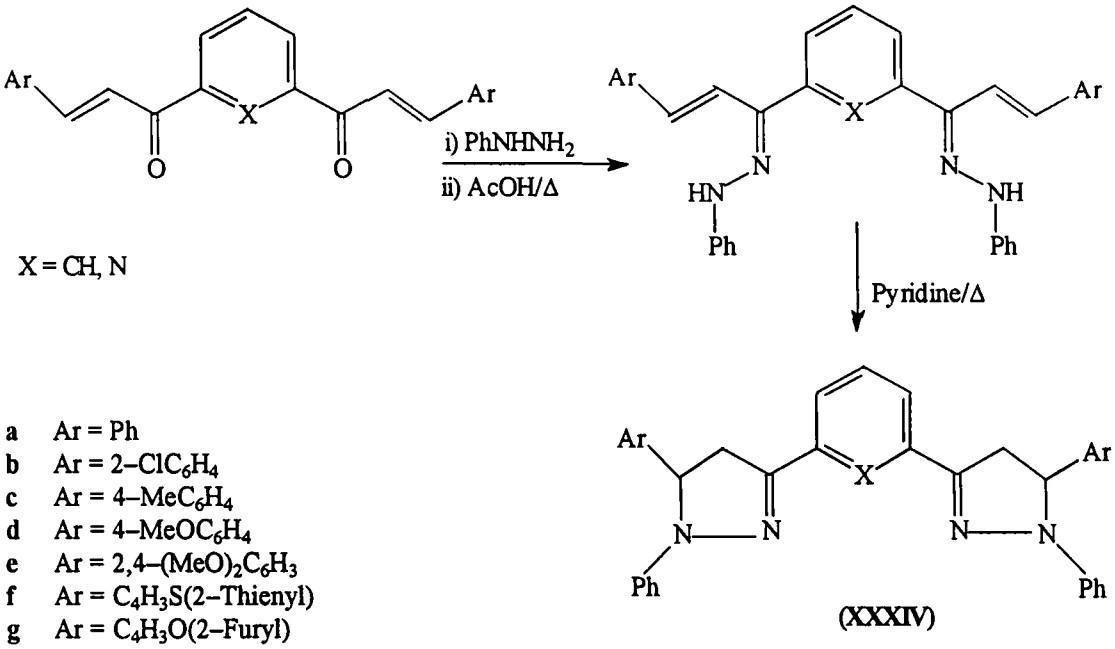
α,α'-Bis[spiro(4-aryl-1-pyrazoline)]cycloalkanones[118,119] (**XXXIII**) have been synthesized through cycloaddition of diazomethane with α,α'-diarylidenecycloalkanones in chloroform



(XXXIII)

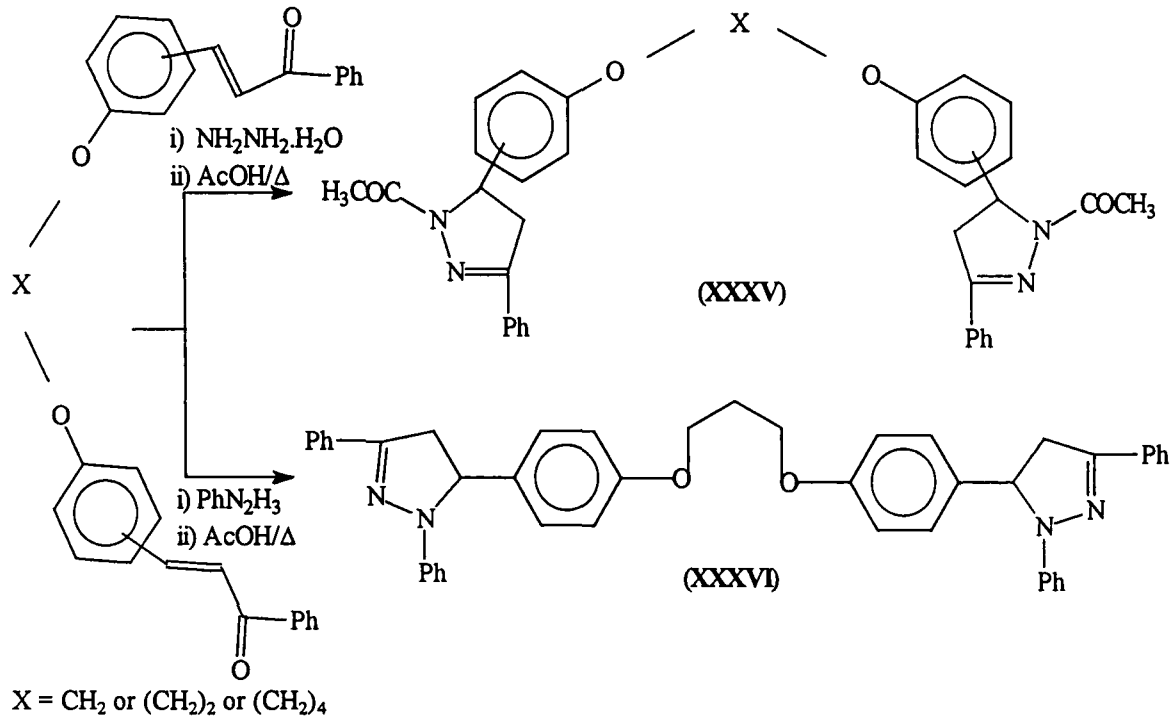
	n	R
a	3	C_6H_5
b	3	3–NO_2–C_6H_4
c	3	3,4–$(OCH_3)_2$.C_6H_3
d	3	2,4–$(OCH_3)_2$.C_6H_3
e	3	3,4–(O_2CH_2).C_6H_3
f	3	4–Cl.C_6H_4
g	3	2–Cl.C_6H_4
h	3	4–$(CH_3)_2$N.C_6H_4
i	3	2–Furyl
j	2	C_6H_5
k	2	3,4–$(OCH_3)_2$.C_6H_3
l	2	2–Furyl
m	2	2–Cl.C_6H_4

F. Al-Omran *et al.*[120-121] have also synthesized bis(2-pyrazoline) derivatives (**XXXIV**) by 2,6-dicinnamoyl pyridines or 1,3-dicinnamoyl-benzenes with phenyl hydrazine.

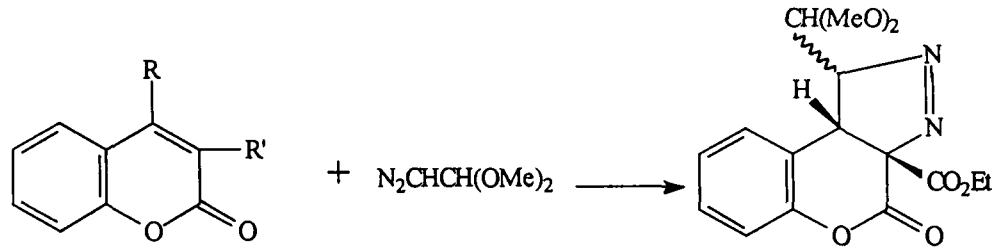


(XXXIV)

A.H.M. Elwahy[122] have prepared bis(4,5-dihydropyrazolyl) ethers (**XXXV**) by condensation of bis(chalcones) with hydrazine hydrate/phenyl hydrazine in acetic acid.



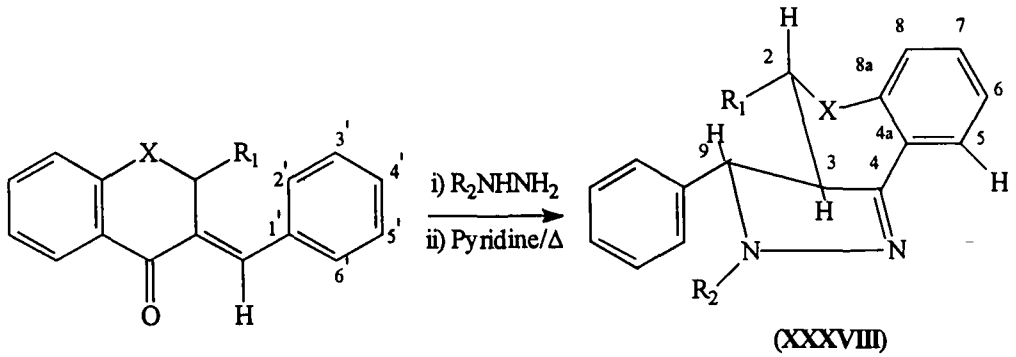
Cyclization of coumarines with $N_2CHCH(OMe)_2$ give corresponding diastereo fused pyrazolines[123] **(XXXVII)**.



R = H
R' = CO_2Et

(XXXVII)

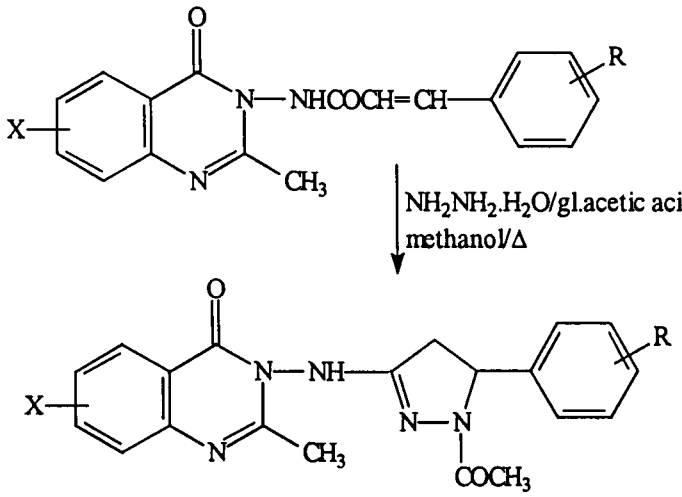
G. Toth and co-workers[124] have synthesized several fused benzopyrano [4.3-c] pyrazolines **(XXXVIII)** by the condensation of the appropriate α,β-unsaturated ketones with methyl or phenyl hydrazines in pyridine.



(XXXVIII)

	X	R_1	R_2
a	CH_2	H	–
b	S	H	–
c	O	H	–
d	O	Ph	–
e	CH_2	H	Ph
f	CH_2	H	Ph
g	S	H	Me
h	S	H	Ph
i	O	H	Me
j	O	H	Ph
k	O	Ph	Me
l	O	Ph	Ph

Archana *et al.*[134] have synthesized 1-acetyl-5-substituted aryl-3-(3'-amino-2'-methyl-6'-monosubstitutedquinazoline-4'(3'H)-onyl]-2-pyrazolines **(XXXIX)** by heating 1-[3'-amino-2'-methyl-6'-monosubstitutedquinazolin-4'(3'H)-onyl]-3-(arylidenyl)chalcones by cycloaddition of hyrazine hydrate in methanol and these were tested for anticonvulsant activity.

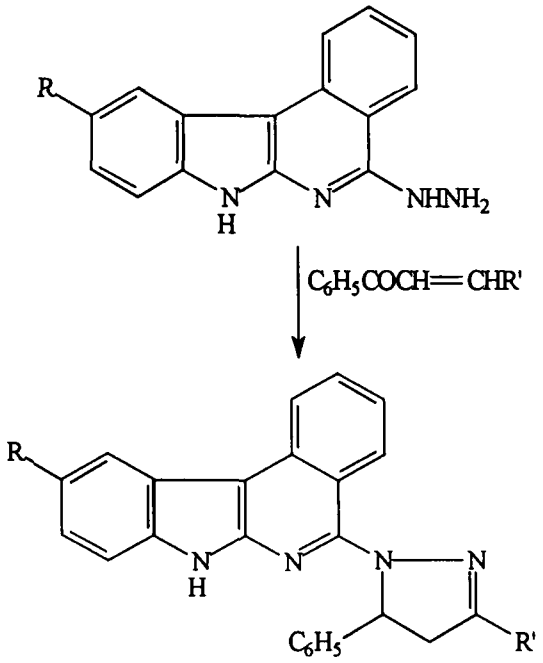


(XXXIX)

	R	X
1	H	H
2	*p*-OMe	H
3	*p*-OH	H
4	*p*-N(Me)$_2$	H
5	*m*-OMe, *p*-OH	H
6	H	6-Br
7	*p*-OMe	6-Br
8	*p*-OH	6-Br
9	*p*-N(Me)$_2$	6-Br
10	*m*-OMe, *p*-OH	6-Br

	R	X
1	H	H
2	*p*-OMe	H
3	*p*-OH	H
4	*p*-N(Me)$_2$	H
5	*m*-OMe, *p*-OH	H
6	H	6-Br
7	*p*-OMe	6-Br
8	*p*-OH	6-Br
9	*p*-N(Me)$_2$	6-Br
10	*m*-OMe, *p*-OH	6-Br

S.P. Hiremath *et al.*[135] have prepared 1-(10-substituted-7H-indolo[2,3-*c*]isoquinolin-5-yl)-3,5-disubstituted pyrazolines **(XXXX)** by refluxing 5-hydrazino-10-substituted-7H-indolo[2,3-*c*] isoquiolines with appropriate arylideneacetophenones in ethanol.



(XXXX)

	R	R'
a	Cl	C_6H_5
b	Me	C_6H_5
c	Br	C_6H_5

Discussion

DISCUSSION

SUMMARY

The work described in this chapter includes the reaction of thiosemicarbazide with -

*(i) 1,5-Bis(3,4-dimethoxyphenyl)pent-1,4-dien-3-one **(4)** which afforded a novel compound, 2-[3-{(3,4-dimethoxyphenyl)ethenyl}-5-{(3,4-dimethoxyphenyl)}-2-pyrazolin-1-yl]thiocarboxamide **SD_5 (12)**. The thiosemicarbazone **(11)** formed as intermediate being minor could only be detected on TLC (R_f value, shade).*

*(ii) 1,5-Bis(4-chlorophenyl)pent-1,4-dien-3-one **(8)** which yielded an analogous compound, 2-[3-{2-(4-chlorophenyl)ethenyl}-5-{(4-chlorophenyl)}-2-pyrazolin-1-yl]thiocarboxamide **SD_{4A} (14)** and thiosemicarbazone, N^1-[1,5-bis(4-chlorophenyl)pent-1,4-dien-3-ylidene]thiosemicarbazide **SD_4 (13)** as intermediate, both (i & ii) in the presence of hydrochloric acid and*

*(iii) 1,5-Bis(4-methylphenyl)pent-1,4-dien-3-one **(15)** in the presence of acetic acid which yielded the thiosemicarbazone, N^1-[1,5-bis(4-methylphenyl)pent-1,4-dien-3-ylidene]thiosemicarbazide **SD_2 (16)** as the sole product. When this reaction failed to cyclise in acetic acid, the above reactions (i) and (ii) have then been carried out in HCl.*

*Structures are established on the basis of IR, Mass, ^{1}H-NMR and ^{13}C-NMR spectral studies. The compounds **(12)** and **(14)** have been evaluated for anticancer activity and compound **(12)** for antibacterial activity.*

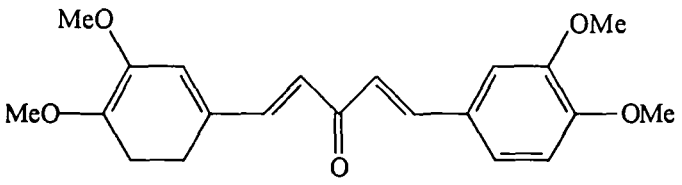
INTRODUCTION

The synthesis of 2-pyrazolines has received considerable attention because of their wide range of applications as antibacterial[6-15], antifungal[16-26], insecticidal[27-29], antiinflammatory[47-58], analgesic[48,59] antipyretic, antiallergic[65], antihistaminic[66], diuretic[67], antiviral[69], (antitumor activity and anti-HIV)[70-71], antidepressant[72-73], hypoglycemic activity[74-75], hypotensive[80-82]

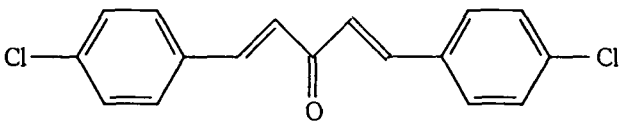
and cerebroprotective agents[83-85], anticonvulsant[114] and local anesthetic[114,125] and also industrial applications as activators for polymerization[126], dyes for wool, nylon[127], electrophotographic photoconductors[128], wavelength shifters in liquid, polymer scintillation[129] and optical brightners[130]. The reactions of a number of α,β-unsaturated ketones with hydrazines forming pyrazolines are reported.[81,99-104] Recently, two groups of researchers, M.E. Elba[131] and Bela Rezessy *et al.*[132] have also carried out reactions of chalcones with thiosemicarbazide to form pyrazolines. However, the analogous reactions with α,β–unsaturated dienones have not yet been described. Keeping in view of the above findings and as part of our work in search of biologically active sulphur and nitrogen containing heterocycles, we have undertaken this problem. It consists of the reactions of dienones (i) *1,5-bis(3,4-dimethoxyphenyl)pent-1,4-dien-3-one* **(4)** and (ii) *1,5-bis(4-chlorophenyl)pent-1,4-dien-3-one*(**8**) with thiosemicarbazide in the presence of hydrochloric acid which yielded *novel compounds*, *2-[3-{2-(3,4-dimethoxyphenyl)ethenyl}-5-{(3,4-dimethoxyphenyl)}-2-pyrazolin-1-yl]thiocarboxamide* **(12)**, and *2-[3-{2-(4-chlorophenyl)ethenyl}-5-{(4-chlorophenyl)}-2-pyrazolin-1-yl]thiocarboxamide* **(14)**. In the former, the thiosemicarbazone **(11)** formed as intermediate being minor could not be isolated while in the latter, the thiosemicarbazone, *N^1-[1,5-bis(4-chlorophenyl)pent-1,4-dien-3-ylidene]thiosemicarbazide* **(13)** was isolated in 10% yield. (iii) The reaction of the dienone, *1,5-bis(4-methylphenyl)pent-1,4-dien-3-one* **(15)** with thiosemi-carbazide has been carried out in the presence of acetic acid in which the corresponding thiosemicarbazone, *N^1-[1,5-bis(4-methylphenyl)pent-1,4-dien-3-ylidene] thiosemicarbazide* **(16)** formed could not cyclize to give the desired product. Due to the failure of this reaction in acetic acid medium, the above two reactions (i & ii) have then been carried out in the presence of hydrochloric

acid. The dienones **(4)**, **(8)** and **(15)** have been prepared following a reported method[133] by condensing acetone with benzaldehydes (molar ratio, 1:2) in the presence of 2.5 equivalents of sodium hydroxide.

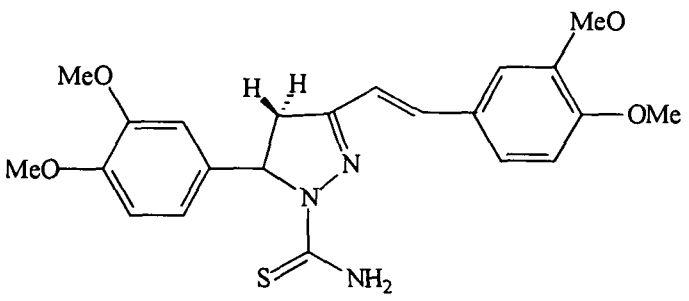
Structural assignments, stereochemistry and biological assay are discussed. Screening results of compounds **(12)** and **(14)** are summarized for anticancer activity against 3-cell lines of three types of human cancers : lung, breast and CNS. Screening results of **(12)** are also summarized for antibacterial activity against four bacteria *Escherichia coli*, *Bascillus subtilis*, *Staphylococcus epidermatis* and *Streptococcus viridans* **(DETAILS IN CHAPTER-6)**.



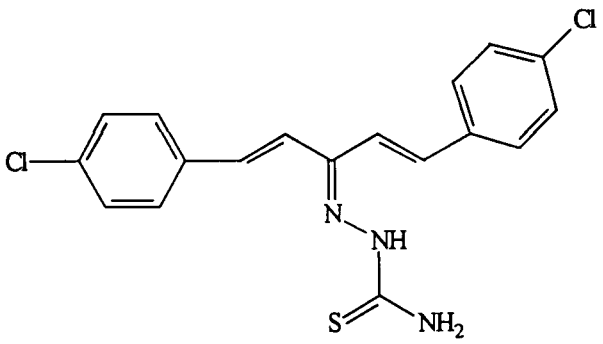
(4)



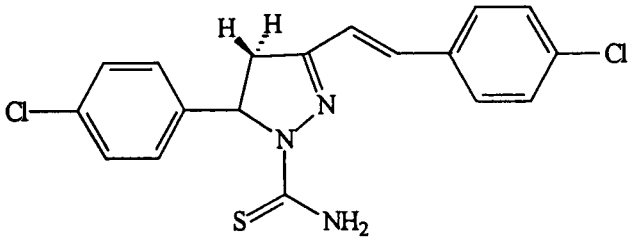
(8)



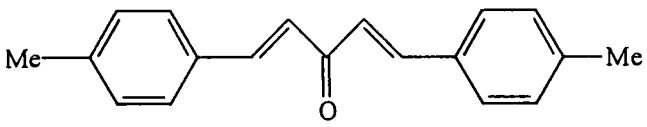
(12)



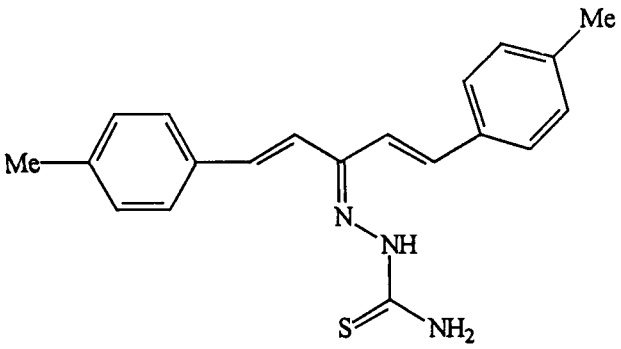
(13)



(14)



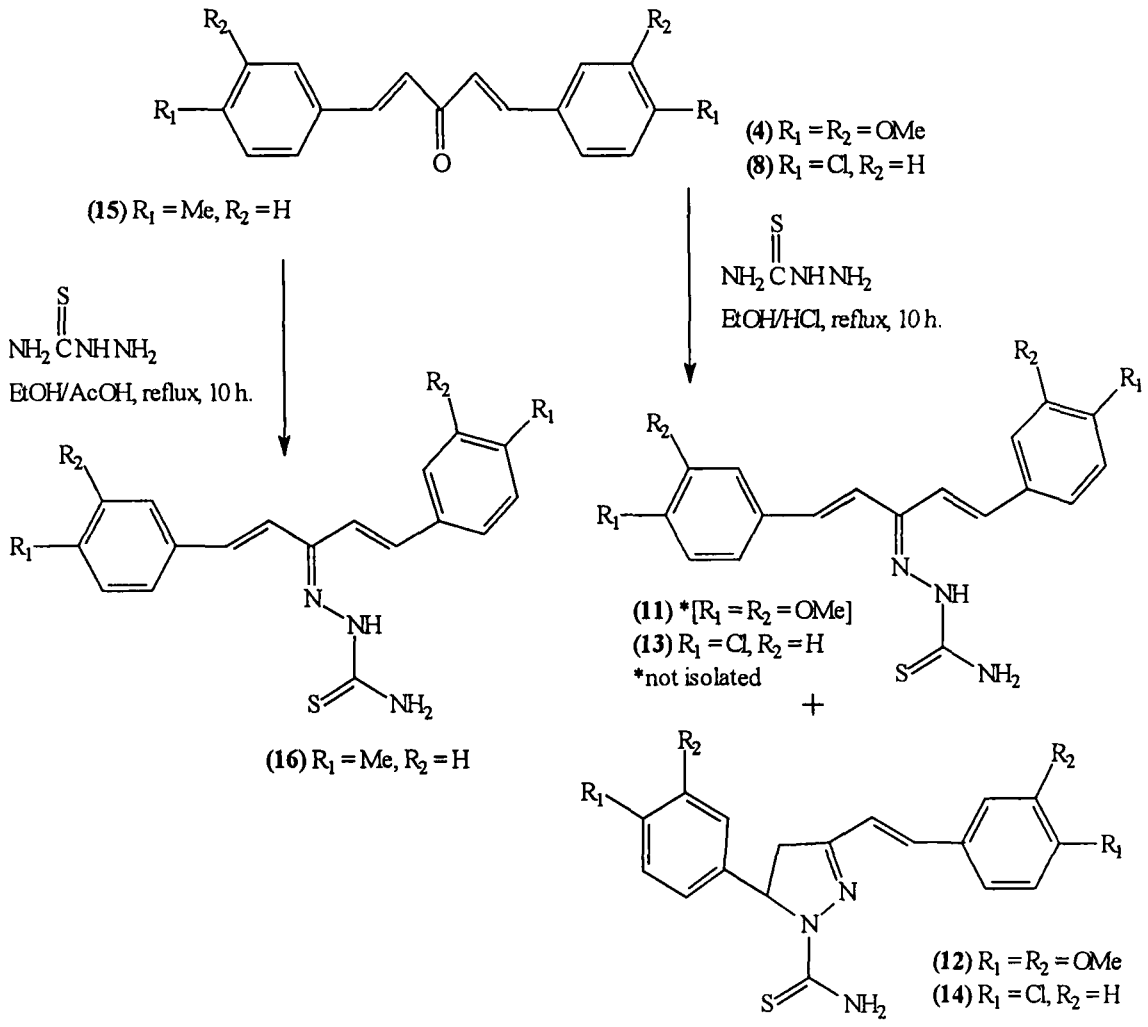
(15)



(16)

RESULTS AND DISCUSSION

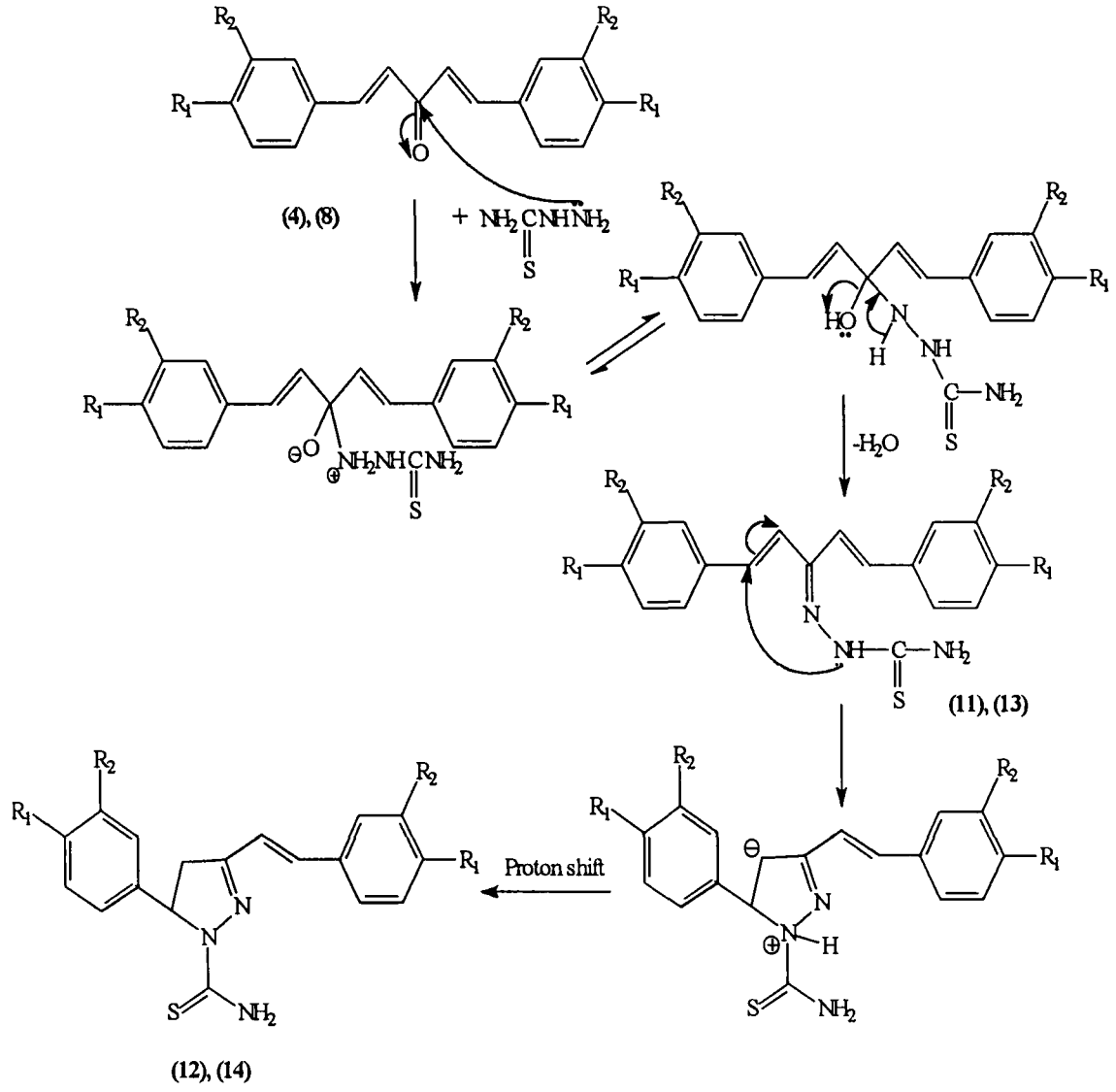
The syntheses of compounds (12) and (14) were carried out from the corresponding dienones (4) and (8) by reaction with thiosemicarbazide (molar ratio, 1:3) in the presence of catalytic amount of conc. hydrochloric acid refluxing in ethanol for 10 h. In the former reaction, the uncyclized thiosemicarbazone (11)* was so minor that it could only be detected on TLC while in the latter, the uncyclized thiosemicarbazone (13) was obtained in 10% yield. The reaction of dienone (15) was performed in AcOH medium where the thiosemicarbazone (16) formed could not cyclize (SCHEME - III).



SCHEME - III

Mechanism of the above reactions :

A plausible mechanism for the above reactions may be depicted as shown in **SCHEME-IV**. The 2-pyrazolines **(12)** and **(14)** are believed to be formed via condensation of the thiosemicarbazide with the carbonyl group of dienones **(4)** and **(8)** and subsequent cyclization of the so formed thiosemicarzones **(11)** and **(13)**.

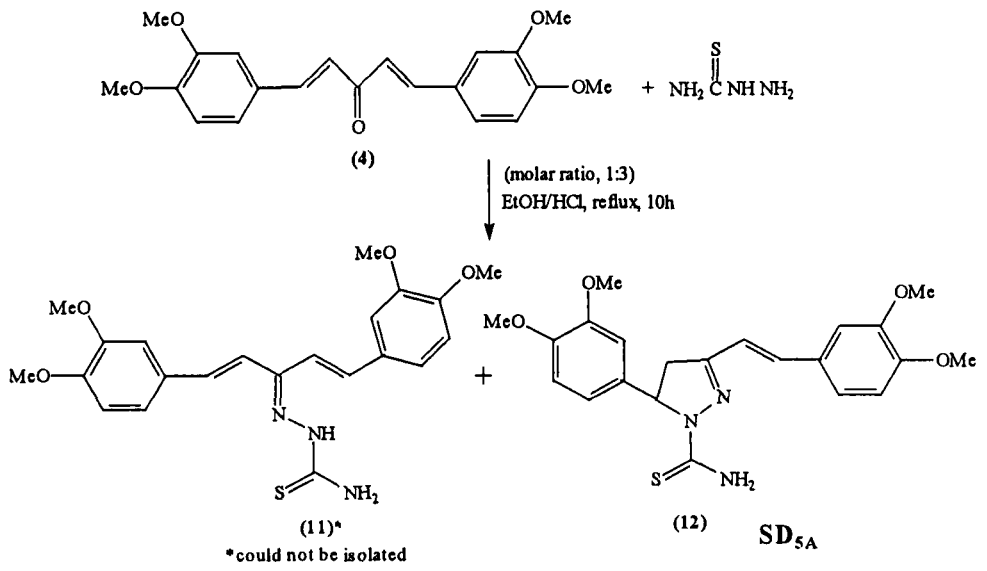


SCHEME-IV

(i) Reaction of 1,5-bis(3,4-dimethoxyphenyl)pent-1,4-dien-3-one (4) with thiosemicarbazide in the presence of catalytic amount of conc. HCl. [Synthesis of 2-[3-{(3,4-dimethoxyphenyl)ethenyl}-5-{(3,4-dimethoxyphenyl)}-2-pyrazolin-1-yl]thiocarboxamide SD_{5A} (12)]

A mixture of *1,5-bis (3,4-dimethoxyphenyl)pent-1,4-dien-3-one* (4) and thiosemicarbazide (molar ratio, 1:3) in ethanol in the presence of a few drops of concentrated hydrochloric acid was refluxed with stirring for 10 h. TLC examination (silica gel 'G', benzene-ethylacetate, 8:2 v/v) of the reaction mixture showed the formation of two components, one very minor (upper) and other major (lower) which was labelled as **SD_{5A}**. After usual work up, the residue was subjected to column chromatography over silica gel using benzene-ethyl acetate (8:2 v/v) as eluent. Elution of the column first furnished a minor orange-coloured product which was detected by TLC examination to be expected thiosemicarbazone **(11)** by comparing with the thiosemicarbazone **SD_4 (13)** (R_f and shade). The minor product (11) could not be recovered. Further elution of the column yielded a dark brown solid which on crystallization from benzene-acetone furnished **SD_{5A}** as brown crystalline needles in 65% yield.

The reaction sequence is given below -



Structure Elucidation of SD_{5A} (12)

It is a brown needle shaped crystalline solid, m.p. 130 °C and appears dark brown on exposure to iodine vapours (TLC). The structure of **SD_{5A}** has been elucidated by FT-IR, DCI-MS, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum (KBr) displayed characteristic bands at 3447, 3338 (NH), 2934, 2834 (CH), 1659 (C=C), 1589 (C=N), 1513, 1465 (phenyl), 1345 (C=S), 1261, 1136 (C-O-C), 1020 (C-N), 961, 805, 759, 612 cm^{-1}. The DCI-MS (NH_3 as reagent gas) of **SD_{5A}(12) (FIG. 25)** showed $[M+H]^+$ peak as the base peak at m/z 428 (100.0) confirming its molecular weight as 427 [$C_{22}H_{25}O_4N_3S$] which is equal to the sum of molecular weights of *1,5-bis(3,4-dimethoxyphenyl)pent-1,4-dien-3-one* (**4**) (354) and thiosemicarbazide (91) minus one molecule of water (18). This indicated that the condensation has occurred between *1,5-bis(3,4-dimethoxyphenyl)pent-1-4-dien-3-one* (**4**) and thiosemicarbazide. A peak at m/z 394 was obtained by the loss of one molecule of H_2S $[(M+1) - H_2S]^+$ and a peak at m/z 368 by the loss of $CSNH_2$ $[(M+1) - CSNH_2]^+$. The peak at m/z 352 $[(M+1) - NH_2CSNH_2]^+$ arised by the cleavage of 1-2 and 1-5 bonds, appeared to be the diagnostic peak of pyrazoline ring and a peak at m/z 237 $[(M+1) - C_{11}H_{13}NO_2]^+$, all supported the deduced structure. The mode of fragmentation is presented in **CHART-8.** The ^{1}H-NMR **(FIG. 26)** and ^{13}C-NMR **(FIG. 27)** spectra of **SD_{5A}** dissolved in acetone-d_6 showed signals as assigned **(TABLE-9)**. The assignments of all ^{1}H-NMR and ^{13}C-NMR signals to individual H- and C-atoms have been performed on the basis of typical chemical shift values, multiplicity, relative integrations and by comparing spectral data with similar compound **SD_{4A}** **(TABLE-10)**. The ^{1}H-NMR spectrum of compound **SD_{5A}(12)** revealed the presence of three double doublets represented by a typical ABX splitting pattern due to geminal and vicinal coupling of the two diastereotopic protons

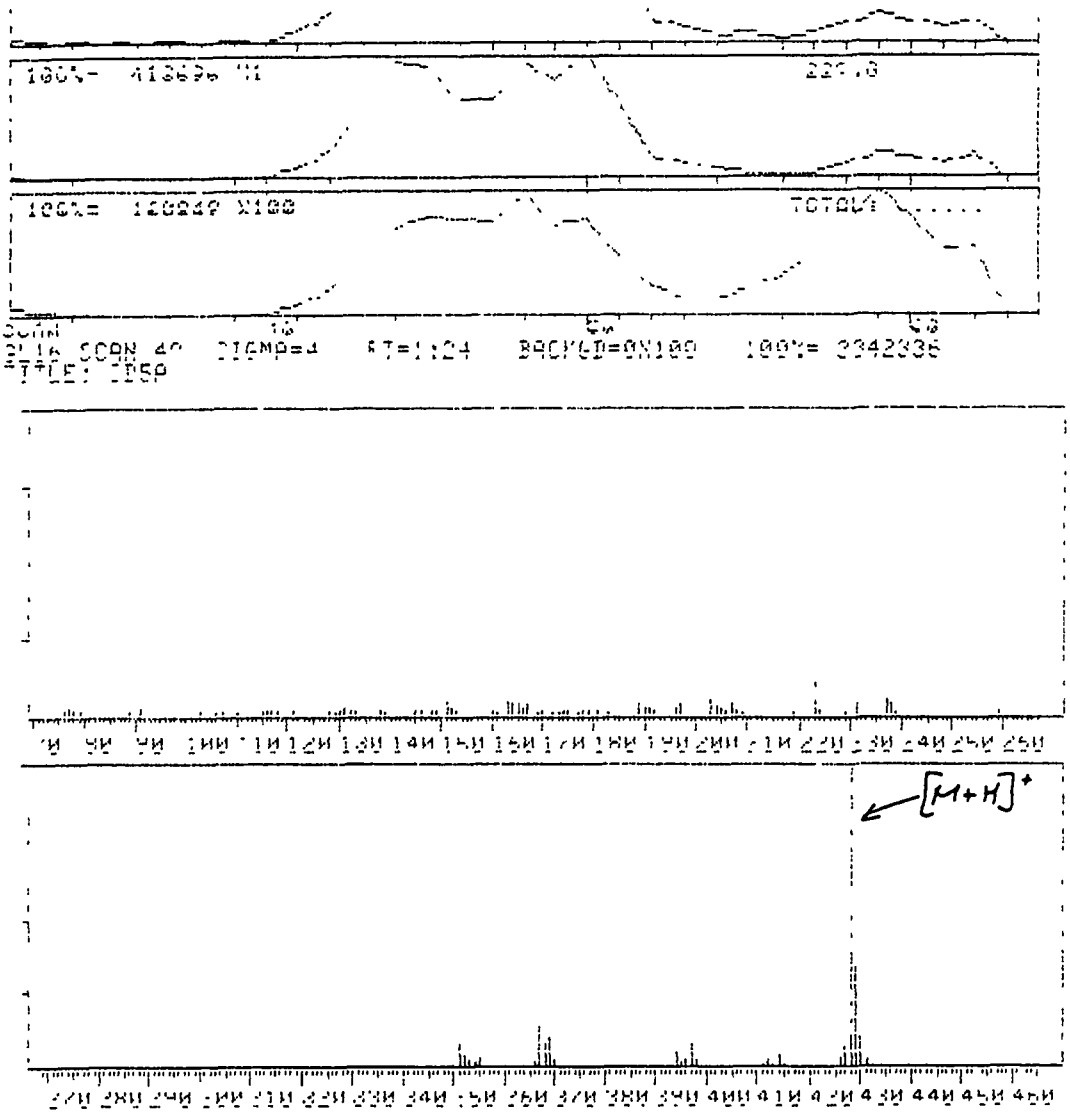


FIG. 25

GL16 SCAN 48 SIGMA=4 RT=1 24 BACKGD=0X100 100%= 3342336
TITLE SDSA

	151 00	7 3	237 00	5 4	369 00	10 7	428.00	100 0
	157 00	4 6	291 00	7 3	394 00	6 3	429 00	34 [illegible]
	164 00	4 2	352 00	5 1	397 00	7 4	430 00	10 [illegible]
	207 00	[illegible]	367 00	13 3	414 00	4 4		
	223 00	11 5	368 00	[illegible]	427 00	[illegible]		

IN

START = 32 END = 55
TOTAL [illegible]
[illegible]

APA

ACQUISITION PARAMETER TABLE

MASS RANGES [illegible]
INTEGRATION TIMES
TYPE OF RUN NON [illegible]

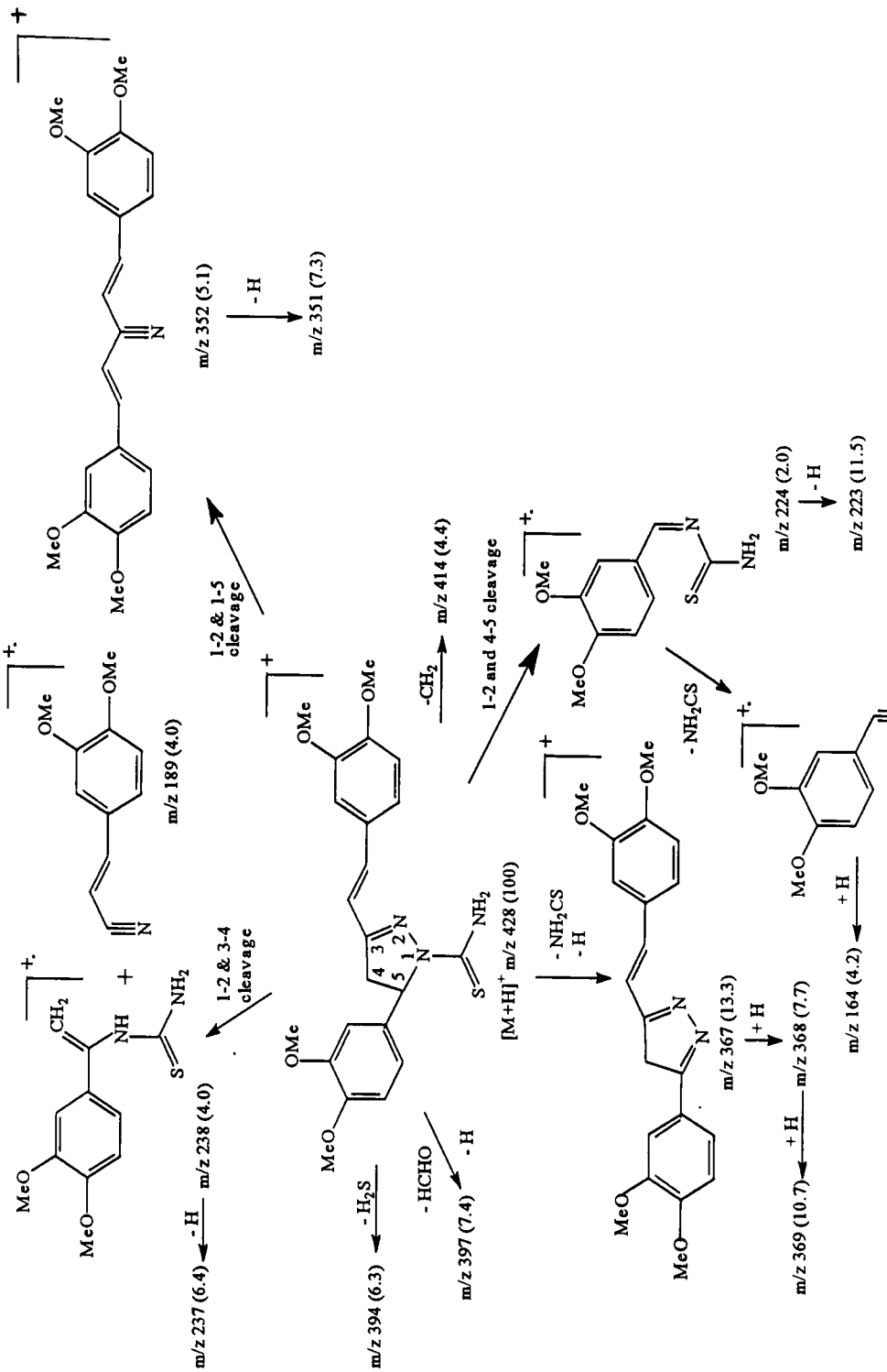

m/z 352 (5.1)
- H
m/z 351 (7.3)
1-2 & 1-5 cleavage
m/z 189 (4.0)
1-2 & 3-4 cleavage
m/z 237 (6.4)
- H
m/z 238 (4.0)
m/z 394 (6.3)
- H2S
- HCHO
m/z 397 (7.4)
- H
-CH2
m/z 414 (4.4)
[M+H]+ m/z 428 (100)
1-2 and 4-5 cleavage
- NH2CS
- H
m/z 367 (13.3)
+ H
m/z 368 (7.7)
+ H
m/z 369 (10.7)
- NH2CS
m/z 224 (2.0)
- H
m/z 223 (11.5)
+ H
m/z 164 (4.2)
m/z 163(4.6)

CHART - 8

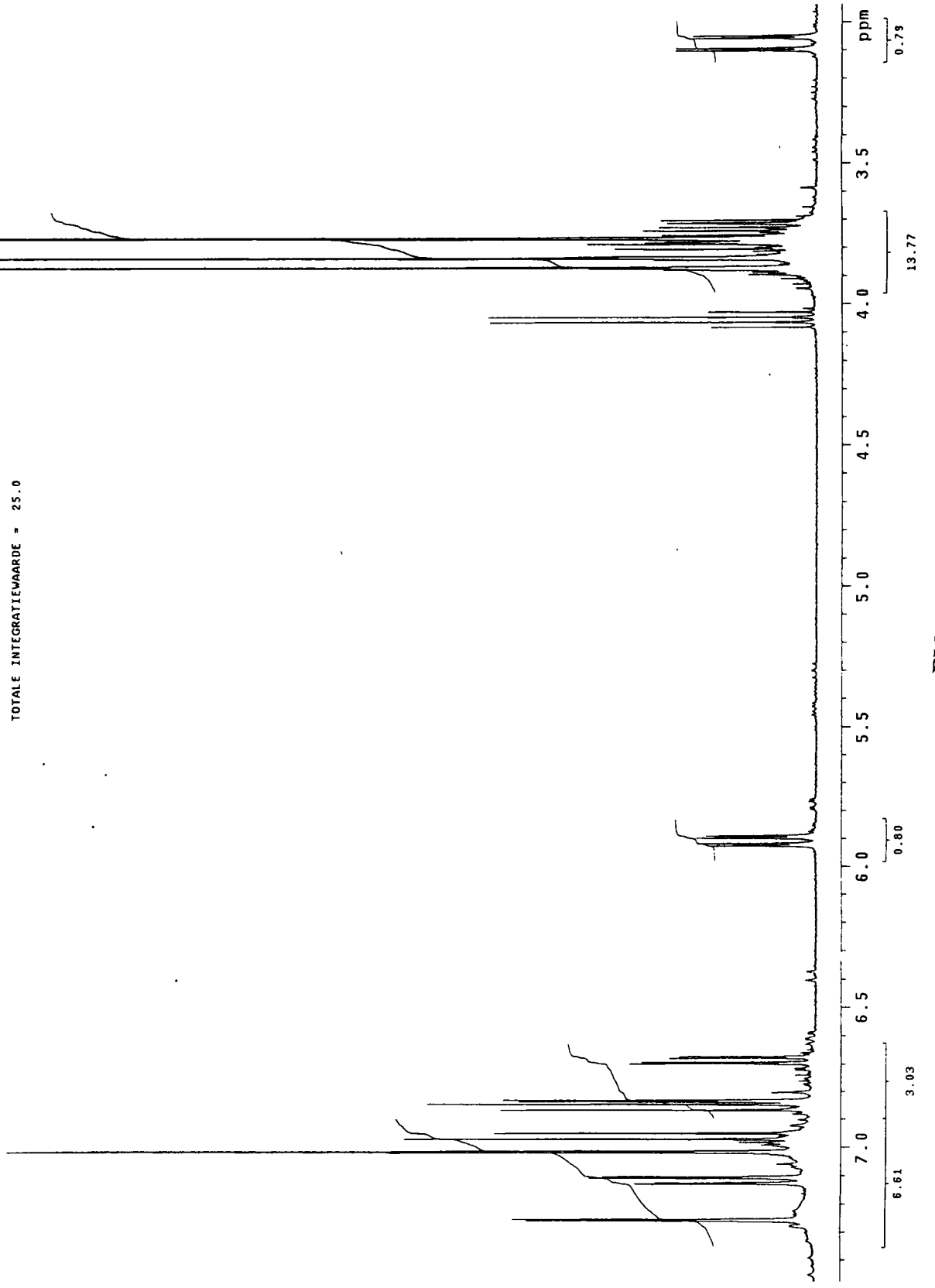
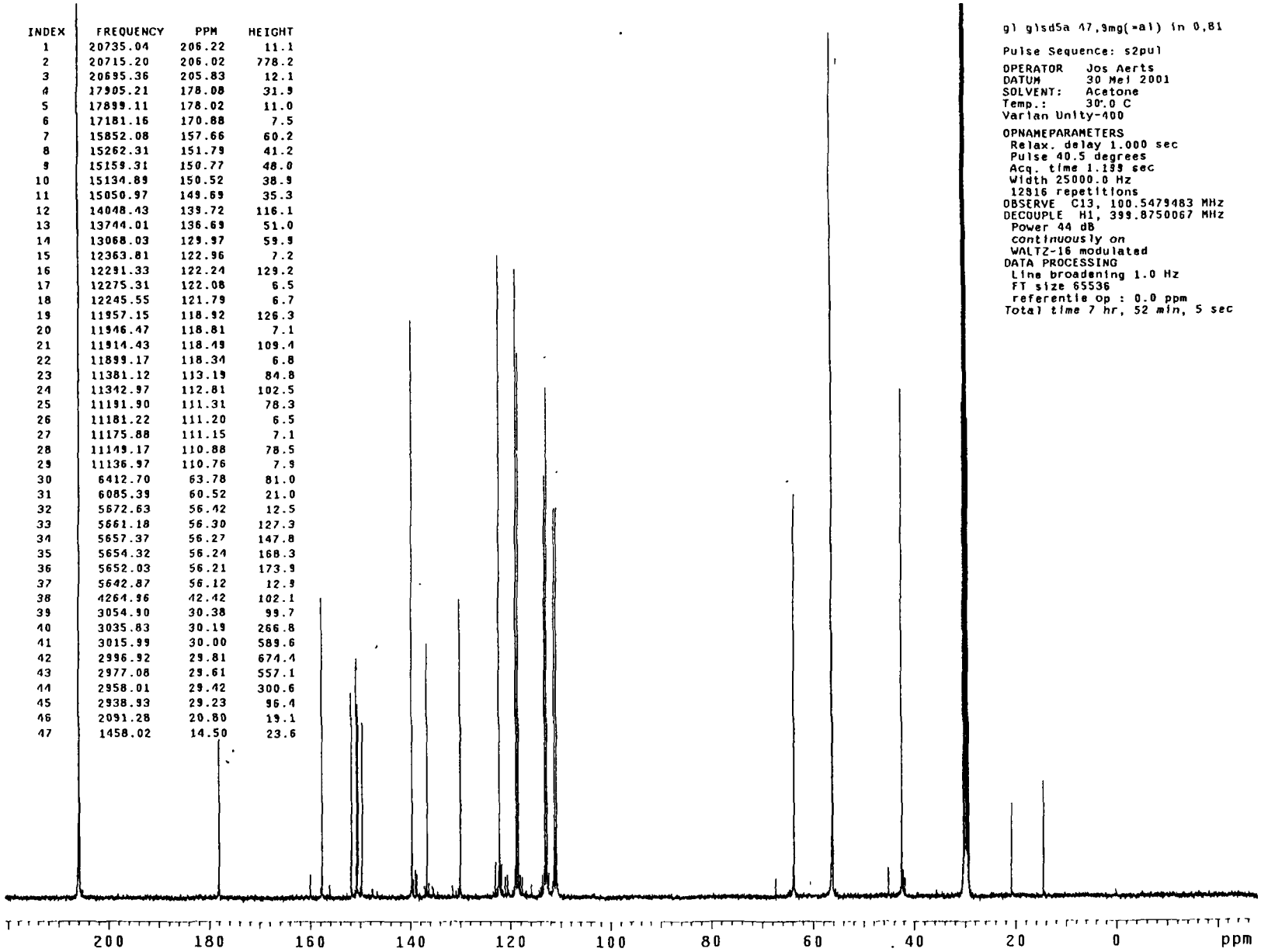

TOTALE INTEGRATIEWAARDE = 25.0
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
6.61
3.03
0.80
13.77
0.79

FIG. 26



INDEX	FREQUENCY	PPM	HEIGHT
1	20735.04	206.22	11.1
2	20715.20	206.02	778.2
3	20695.36	205.83	12.1
4	17905.21	178.08	31.9
5	17899.11	178.02	11.0
6	17181.16	170.88	7.5
7	15852.08	157.66	60.2
8	15262.31	151.79	41.2
9	15159.31	150.77	48.0
10	15134.89	150.52	38.9
11	15050.97	149.69	35.3
12	14048.43	139.72	116.1
13	13744.01	136.69	51.0
14	13068.03	129.97	59.9
15	12363.81	122.96	7.2
16	12291.33	122.24	129.2
17	12275.31	122.08	6.5
18	12245.55	121.79	6.7
19	11957.15	118.92	126.3
20	11946.47	118.81	7.1
21	11914.43	118.49	109.4
22	11899.17	118.34	6.8
23	11381.12	113.19	84.8
24	11342.97	112.81	102.5
25	11191.90	111.31	78.3
26	11181.22	111.20	6.5
27	11175.88	111.15	7.1
28	11149.17	110.88	78.5
29	11136.97	110.76	7.9
30	6412.70	63.78	81.0
31	6085.39	60.52	21.0
32	5672.63	56.42	12.5
33	5661.18	56.30	127.3
34	5657.37	56.27	147.8
35	5654.32	56.24	168.3
36	5652.03	56.21	173.9
37	5642.87	56.12	12.9
38	4264.96	42.42	102.1
39	3054.90	30.38	99.7
40	3035.83	30.19	266.8
41	3015.99	30.00	589.6
42	2996.92	29.81	674.4
43	2977.08	29.61	557.1
44	2958.01	29.42	300.6
45	2938.93	29.23	96.4
46	2091.28	20.80	19.1
47	1458.02	14.50	23.6

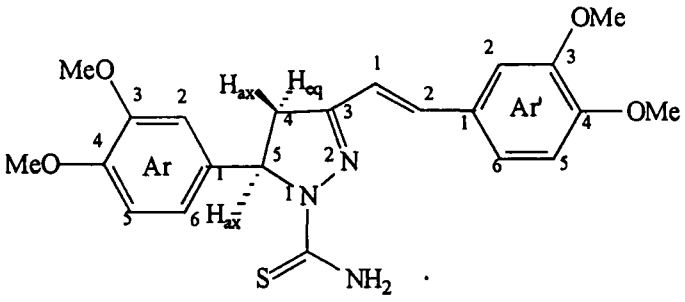
FIG. 27

TABLE -9 : ^{1}H-NMR and ^{13}C-NMR spectral data of SD_{5A} (12)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)	C-nr	δ (ppm)
1'	7.01	1H	d	$J_{1',2'}$=16.48	1'	122.24
2'	7.04	1H	d	$J_{1',2'}$=16.48	2'	139.72
4_{eq}	3.08	1H	dd	$J_{4eq,4ax}$=17.55, $J_{4eq,5ax}$=3.21	3	157.66
4_{ax}	3.76	1H	dd	$J_{4eq,4ax}$=17.55, $J_{4ax,5ax}$=11.29	4	42.42
5_{ax}	5.91	1H	dd	$J_{4eq,5ax}$=3.21, $J_{4ax,5ax}$=11.29	5	63.78
4 x OCH_3	3.76-3.88	12H	s	–	Ar-1	136.69
					Ar-2	111.31
Ar-2	6.84	1H	d	$J_{Ar-2,6}$=2.14	Ar-3	151.79
Ar-5	6.86	1H	d	$J_{Ar-5,6}$=8.24	Ar-4	150.52
Ar-6	6.69	1H	dd	$J_{Ar-2,6}$=2.14 $J_{Ar-5,6}$ = 8.24	Ar-5	113.90
Ar'-2	7.26	1H	d	$J_{Ar'-2,6}$=2.14	Ar-6	118.92
Ar'-5	6.96	1H	d	$J_{Ar'-5,6}$=8.24	Ar'-1	129.97
Ar'-6	7.12	1H	dd	$J_{Ar'-2,6}$=2.14 $J_{Ar'-5,6}$=8.24	Ar'-2	110.88
					Ar'-3	150.77
					Ar'-4	149.69
					Ar'-5	112.81
					Ar'-6	118.49
					> C = S	178.08
					4 x OMe	56.25

(magnetically non-equivalent methylene proton H_A, H_B) at C-4 with the methine proton H_X at C-5 of pyrazoline ring.[132] The two double doublets appeared at δ3.08 and 3.76 with coupling constants (J_{gem}=17.55 Hz, J_{vic}=3.21Hz) in the former and (J_{gem}=17.55 Hz, J_{vic}=11.29 Hz) in the latter due to the coupling with axial proton at C-5 were assigned to equatorial and axial protons of C-4 respectively. The third double doublet at δ5.91 with coupling constants (J=3.21Hz, J=11.29Hz) due to vicinal coupling with two magnetically non-equivalent protons of methylene group at C-4 of pyrazoline ring was assigned to axial methine proton of C-5. The large coupling constant (J=11.29 Hz) of protons at C-4 and C-5 showed that they are trans-oriented (diaxial, antiperiplanar) to each other. The two trans oriented doublets at δ7.01 (J=16.48 Hz) and 7.04 (J=16.48 Hz) were attributed to ethylenic protons at C-1' and C-2' respectively. Thus, coupling constant of ethylenic protons (J=16.48 Hz) indicated their trans geometry. The signals δ3.76, 3.77, 3.84, 3.87 were assigned to four methoxy groups protons. ^{1}H-NMR spectrum also showed significant aromatic signals at δ 6.84 and 6.86 as two doublets with J = 2.14 Hz and J = 8.24 Hz for Ar-2 and Ar-5 protons respectively and a double doublet at δ6.69 with J = 2.14 Hz, J = 8.24 Hz corresponding to Ar-6. Another aromatic signals at δ 7.26 and 6.96 as two doublets with J = 2.14 and J = 8.24 Hz were assigned for Ar'-2, Ar'-5 protons respectively and a double doublet at δ7.12 with J = 2.14 Hz and J = 8.24 was attributed to Ar'-6. The ^{13}C-NMR spectrum of **SD_{5A}** showed the ring carbon signals at δ 136.69 (C-Ar-1), 111.31 (C-Ar-2), 151.79 (C-Ar-3), 150.52 (C-Ar-4), 113.90 (C-Ar-5), 118.92 (C-Ar-6) and δ 129.97 (C-Ar'-1), 110.88 (C-Ar'-2), 150.77 (C-Ar'-3), 149.69 (C-Ar'-4), 112.81 (C-Ar'-5), 118.49 (C-Ar'-6), 56.25 (4 x C-Ar-OCH_3). The ^{13}C-NMR spectral data are thus in agreement with the assigned structure. The ^{1}H-NMR and ^{13}C-NMR spectral data are also in agreement with that of similar functional system.

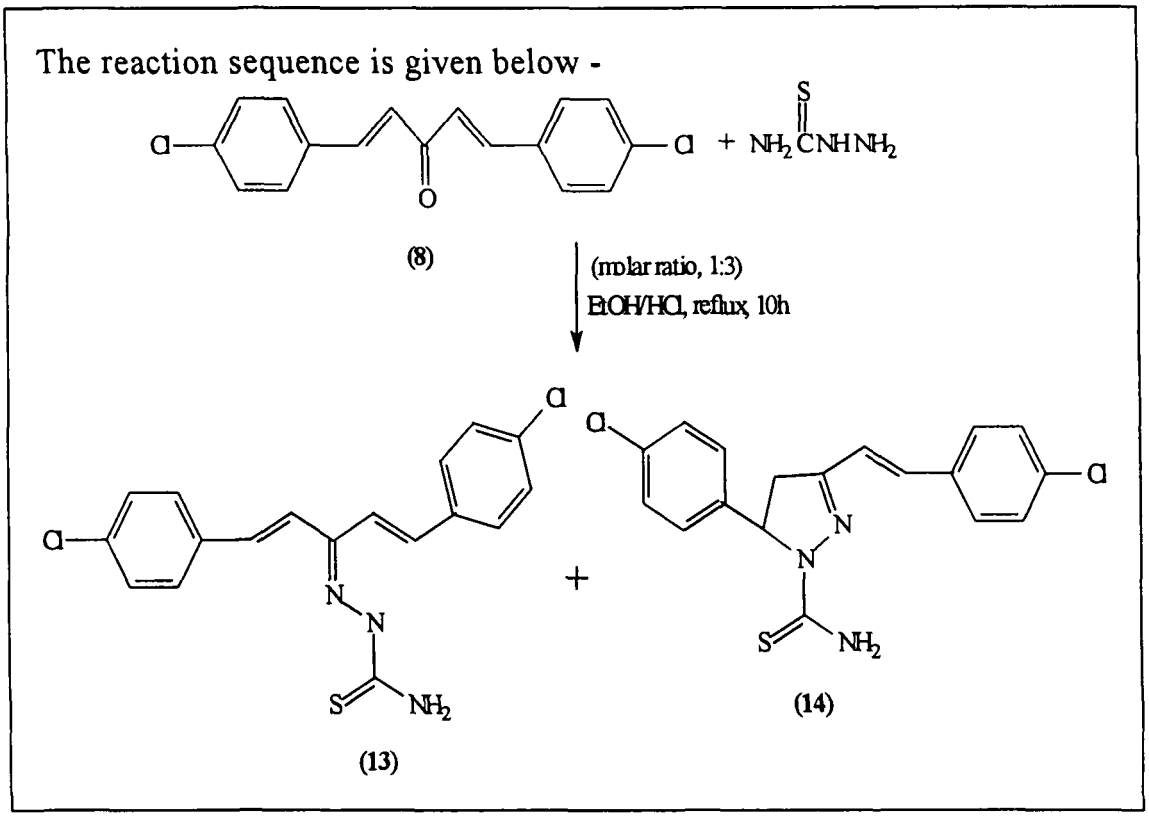
On the basis of above evidence, SD_{5A} was characterized as *2-[3-{(3,4-dimethoxyphenyl)ethenyl}-5-{(3,4-dimethoxyphenyl)}-2-pyrazolin-1-yl]thiocarboxamide (12).*



(12)

(ii) Reaction of 1,5-bis(4-chlorophenyl)pent-1,4-dien-3-one (8) with thiosemicarbazide in the presence of hydrochloric acid [Synthesis of 2-[3-{2-(4-chlorophenyl)ethenyl}-5-{(4-chlorophenyl)}-2-pyrazolin-1-yl]thiocarboxamide SD_{4A} (14). The uncyclized thiosemicarbazone, N^1-[1,5-bis(4-chlorophenyl)pent-1,4-dien-3-ylidene] thiosemicarbazide SD_4 (13) was also obtained in poor yield]

A mixture of *1,5-bis(4-chlorophenyl)pent-1,4-dien-3-one* (8) and thiosemicarbazide (molar ratio, 1:3) in ethanol in the presence of catalytic amount of conc. HCl was refluxed for 10 h. TLC examination (silica gel 'G' benzene-ethylacetate, 8:2 v/v) of the reaction mixture showed the presence of two components, one minor (upper) and the other major (lower), labelled as SD_4 and SD_{4A}. These were separated and purified by column chromatography over silica gel using benzene-ethylacetate (8:2 v/v) as an eluent followed by crystallization (benzene – acetone) to give SD_4 as orange crystalline globules in 10% yield and SD_{4A} as brown crystalline needles in 60% yield.



Structure Elucidation of SD_4 (13)

It is an orange crystalline globules solid, m.p. 130 °C and appears brown on exposure to iodine vapours (TLC). The structure of SD_{4A} has been established by FT-IR, DCI-MS, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum (KBr) displayed characteristic bands 3423, 3247(NH), 1595(C=N), 1497 (Phenyl), 1197 (C=S), 1086 (C–N), 1008, 957, 812 and 708 cm^{-1}. The DCI-MS (NH_3 as reagent gas) spectrum (**FIG. 28**) of SD_4 showed a set of peaks at m/z 376/378/380 (100.0/67.1/13.6) corresponding with $[M+1]^+$, confirming its molecular weights 375/377/379 [$C_{18}H_{15}Cl_2N_3S$] which is equal to the sum of molecular weights of the dienone (8) (302) and thiosemicarbazide (91) minus one molecule of water (18). This indicated that the formation of thiosemicarbazone has occurred by the condensation of (8)

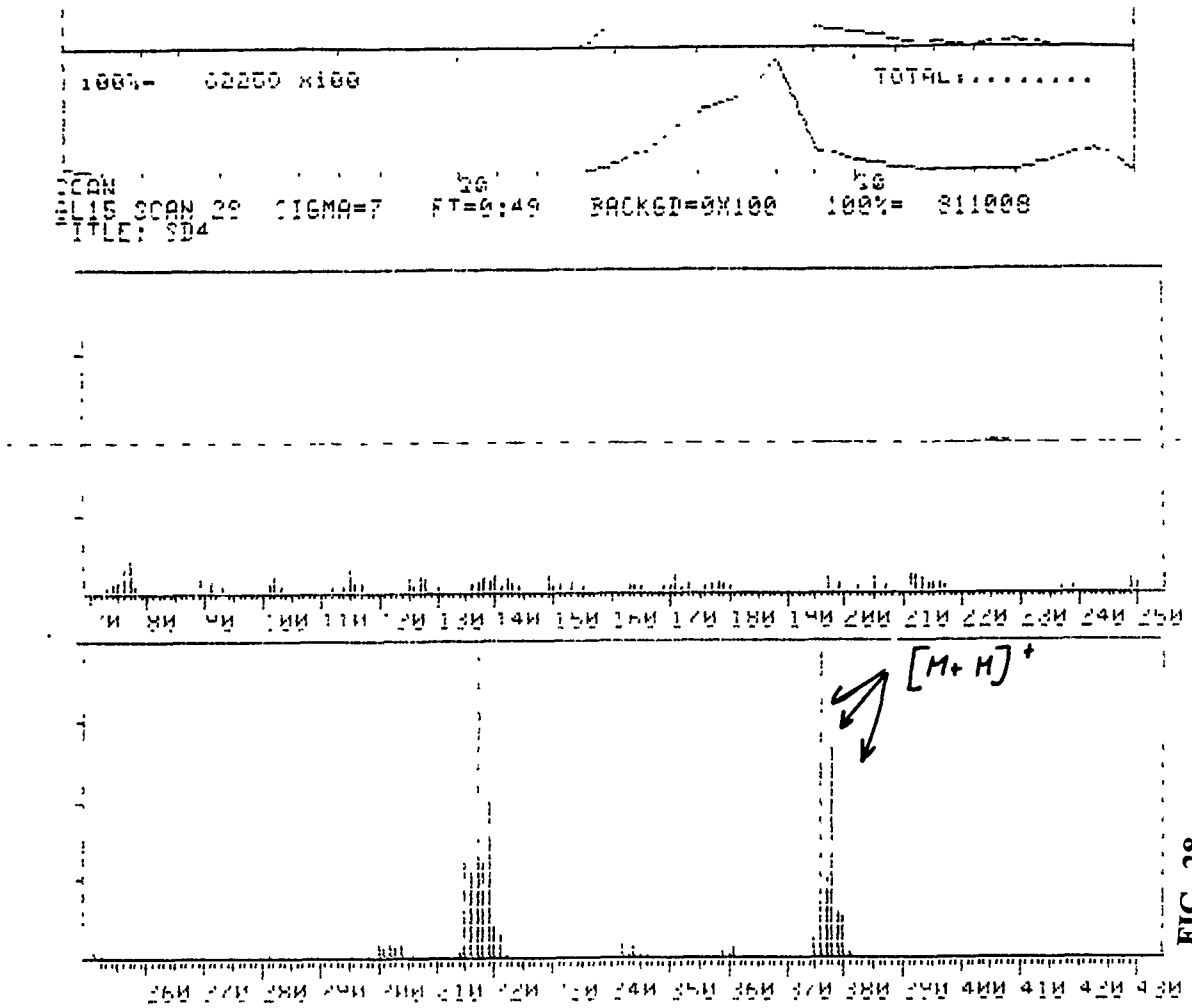


FIG. 28

GL15 SCAN 28 SIGMA=7 RT=0 49 BACKGD=0X100 100%= 311008
TITLE SD4

76 00	7 5	149 00	5 5	304.00	6 5	344.00	4 5
77 00	10 6	171 00	6 5	315.00	30.3	375 00	7 [illegible]
102 00	7 0	197 00	[illegible] 0	316 00	28.7	376 00	100 0
115 00	7 0	205 00	[illegible] 0	317.00	95 9	377.00	[illegible]
125 00	10 6	211 00	[illegible] 0	318 00	30 8	378 00	[illegible] 1
127 00	[illegible]	211 00	[illegible]	319 00	51 0	379 00	14 [illegible]
128 00	4 5	215 00	[illegible]	320 00	11.5	380 00	13 0
138 00	5 0	300 00	[illegible]	321 00	[illegible]		
140 00	6 0	302 00	10 6	342 00	7 0		

IN

START = 10 END = 30

TOTAL	
300 0	4864
317 [illegible]	29312
342 0	3350
359 [illegible]	40%-
376 0	36992

#P4

ACQUISITION PARAMETER TABLE

MASS RANGES 70-550
INTEGRATION TIMES
TYPE OF RUN NON IFS

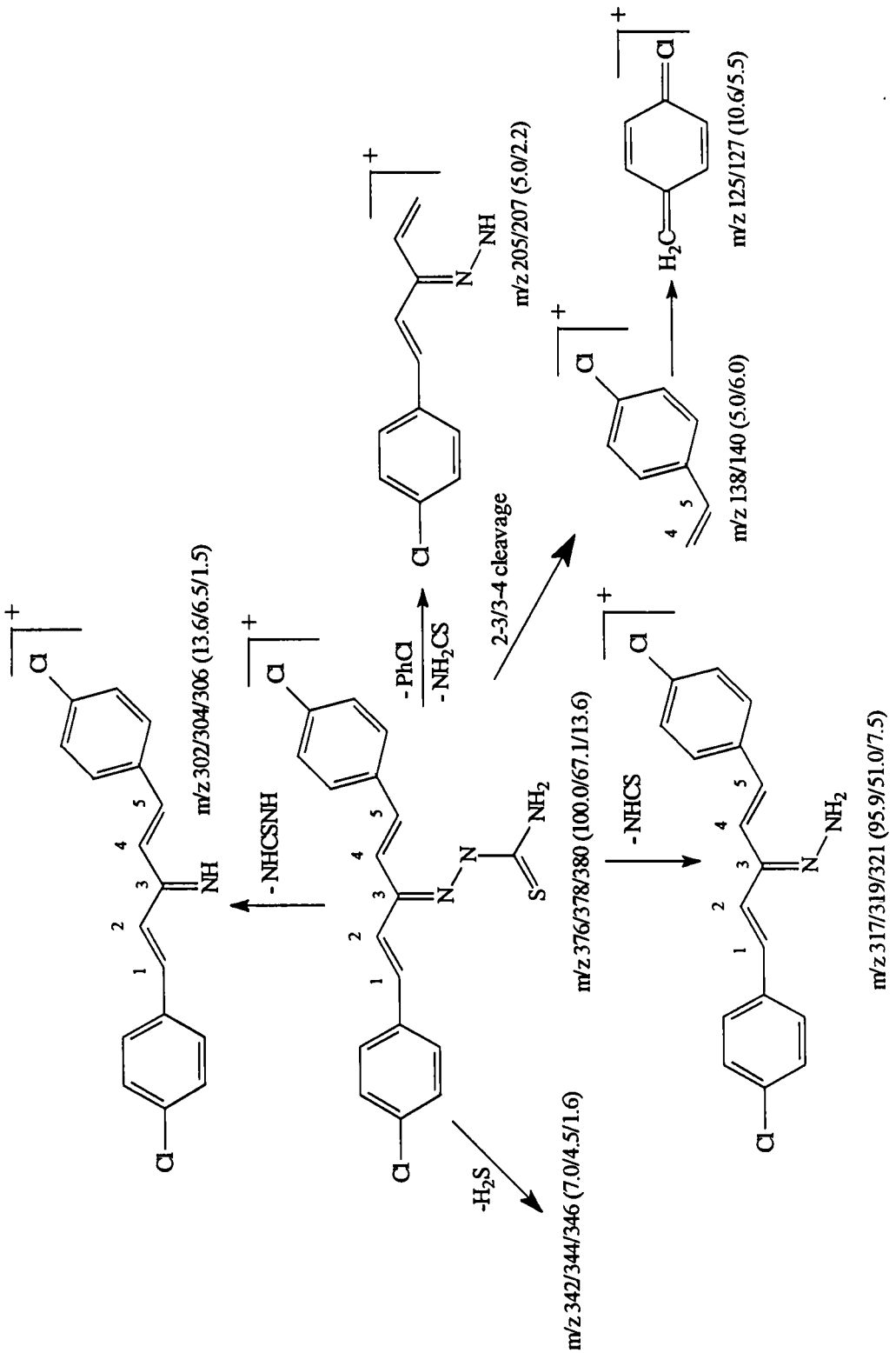

m/z 302/304/306 (13.6/6.5/1.5)
- NHCSNH
- PhCl
- NH2CS
2-3/3-4 cleavage
m/z 205/207 (5.0/2.2)
m/z 342/344/346 (7.0/4.5/1.6)
-H2S
m/z 376/378/380 (100.0/67.1/13.6)
-NHCS
m/z 138/140 (5.0/6.0)
m/z 125/127 (10.6/5.5)
m/z 317/319/321 (95.9/51.0/7.5)

CHART - 9

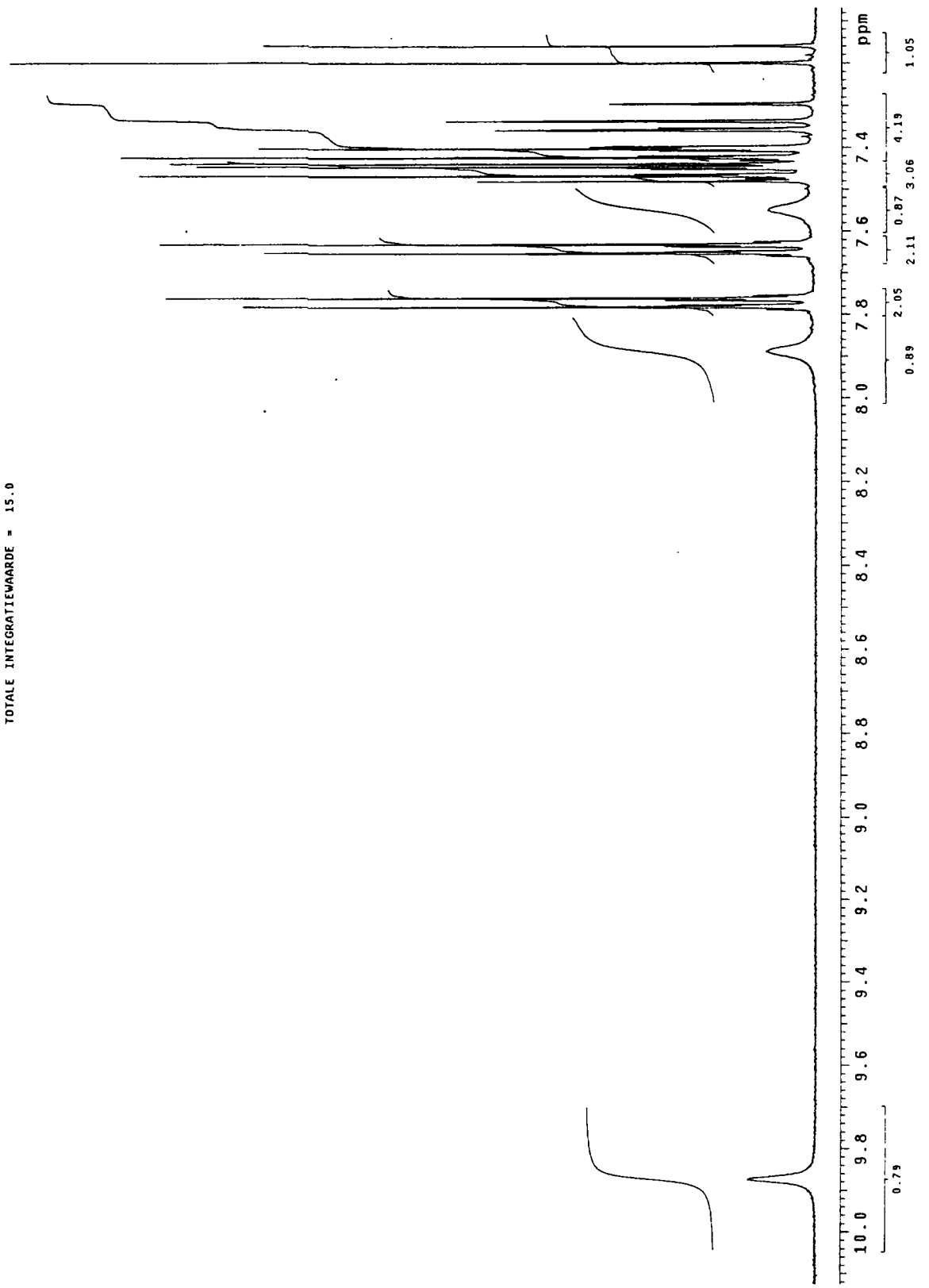

TOTALE INTEGRATIEWAARDE = 15.0
10.0
9.8
9.6
9.4
9.2
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
ppm
0.79
0.89
2.05
2.11
0.87
3.06
4.19
1.05

FIG. 29

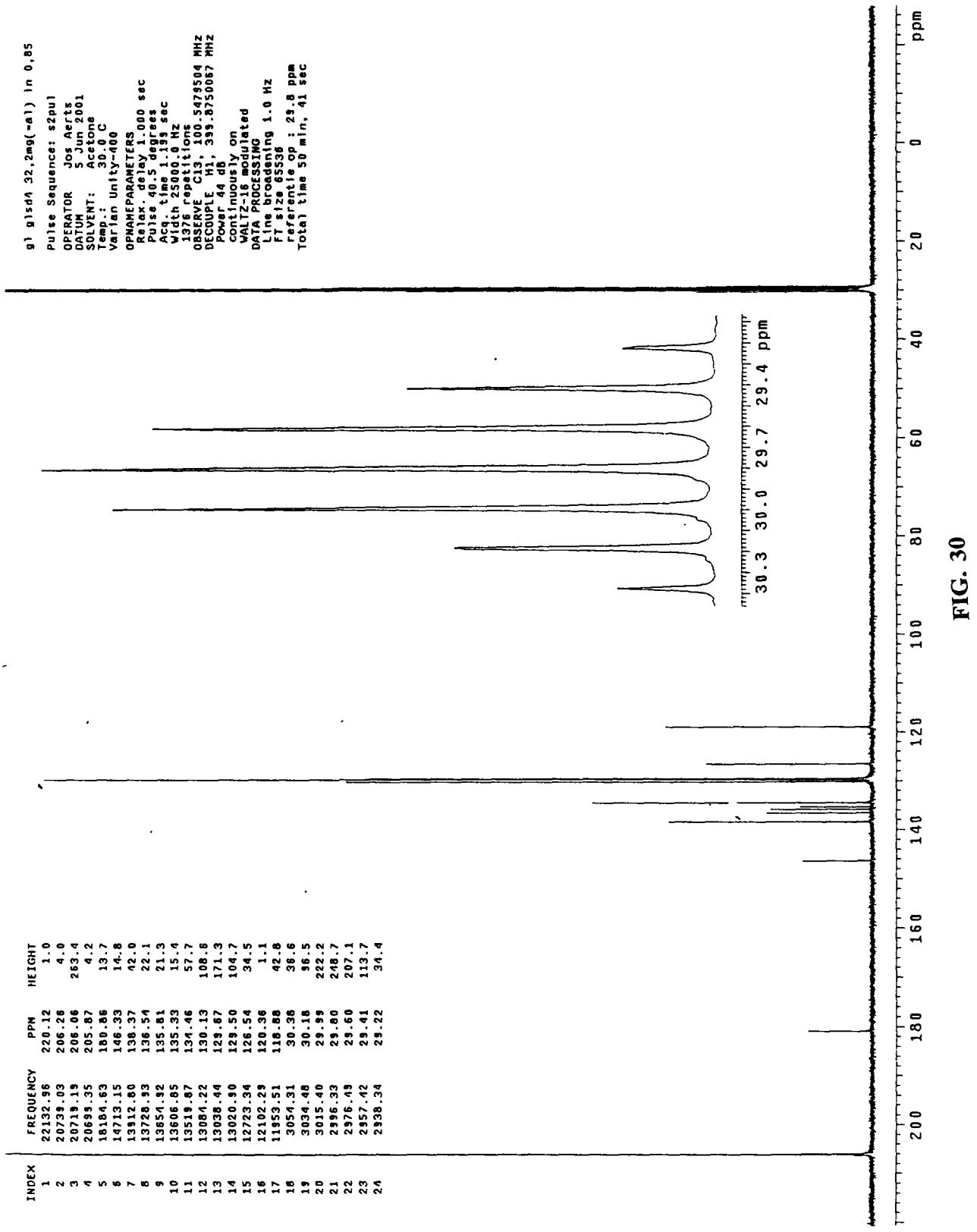

gl glsd4 32.2mg(-al) in 0,85
Pulse Sequence: s2pul
OPERATOR Jos Aerts
DATUM 5 Jun 2001
SOLVENT: Acetone
Temp.: 30.0 C
Varian Unity-400
OPNAMEPARAMETERS
Relax. delay 1.000 sec
Pulse 40.5 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
1376 repetitions
OBSERVE C13, 100.5479504 MHz
DECOUPLE H1, 399.8750067 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
referentie op : 29.8 ppm
Total time 50 min, 41 sec
INDEX FREQUENCY PPM HEIGHT
1 22132.96 220.12 1.0
2 20739.03 206.28 4.0
3 20719.19 206.06 263.4
4 20699.35 205.87 4.2
5 18184.63 180.86 13.7
6 14713.15 146.33 14.8
7 13912.80 138.37 42.0
8 13728.93 136.54 22.1
9 13654.92 135.81 21.3
10 13608.85 135.33 15.4
11 13519.87 134.46 57.7
12 13084.22 130.13 108.6
13 13038.44 129.67 171.3
14 13020.30 129.50 104.7
15 12723.34 126.54 34.5
16 12102.29 120.36 1.1
17 11853.51 118.88 42.8
18 3054.31 30.38 38.6
19 3034.48 30.18 96.5
20 3015.40 29.99 222.2
21 2996.33 29.80 248.7
22 2976.49 29.60 207.1
23 2957.42 29.41 113.7
24 2938.34 29.22 34.4
30.3 30.0 29.7 29.4 ppm
200 180 160 140 120 100 80 60 40 20 0 ppm

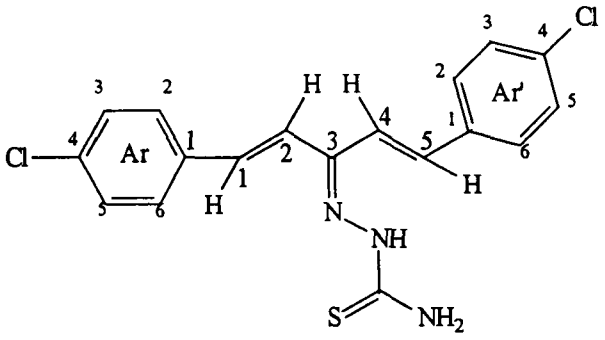
FIG. 30

TABLE -10 : ^{1}H-NMR and ^{13}C-NMR spectral data of SD_4 (13)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)	C-nr	δ(ppm)
1	7.46	1H	d	$J_{1,2}$=16.48	1	138.37
2	7.32	1H	d	$J_{1,2}$=16.48	2	126.54
4	7.18	1H	d	$J_{4,5}$=16.17	3	146.33
5	7.38	1H	d	$J_{4,5}$=16.17	4	118.88
NH	9.87	1H	s	–	5	134.46
NH_2	7.54, 7.90	1H	s	–	Ar+Ar'	129.50-136.54
Ar-2,6	7.77	2H	d	$J_{Ar\text{-}2,6,\ Ar\text{-}3,5}$=8.55	> C = S	180.86
Ar-3,5	7.46	2H	d	$J_{Ar\text{-}2,6,\ Ar\text{-}3,5}$=8.55		
Ar'-2,6	7.64	2H	d	$J_{Ar'\text{-}2,6,\ Ar'\text{-}3,5}$=8.40		
Ar'-3,5	7.41	2H	d	$J_{Ar'\text{-}2,6,\ Ar'\text{-}3,5}$=8.40		

with thiosemicarbazide. The fragment ions corresponding with sets of peaks at m/z 342/344/346 (7.0/4.5/1.6) $[(M+1)-H_2S]^+$, m/z 317/319/321 (95.9/ 51.0/7.5) $[(M+1) - CSNH]^+$ and at m/z 302/304/306 (13.6/6.5/1.6) $[(M+1)-NHCSNH]^+$ supported the thiosemicarbazone structure. The mode of fragmentations is presented in **CHART-9**. The ^1H– and ^{13}C-NMR spectra of **SD_4** dissolved in acetone-d_6 showed signals as assigned (**TABLE-10**). The assignments of all ^1H–NMR **(FIG. 29)** and ^{13}C-NMR **(FIG. 30)** signals to individual H– and C–atoms have been performed on the basis of typical chemical shift values, multiplicity, relative integrations and by comparison with the spectral data of its precursor **(8)**. The ^1H-NMR spectrum of **SD_4** exhibited two doublets at δ 7.32 and δ 7.46 with large coupling constants (J=16.48 Hz) assigned to protons at C-2 and C-1 and other two doublets at δ7.18 and δ7.38 with coupling constants (J=16.48 Hz) attributed to protons at C-4, C-5 respectively. The large coupling constants (J=16.48 Hz) of vicinal protons confirmed their trans dispositions. The protons at C-1 and C-5 appeared at lower fields (δ7.46 and δ7.38) as compared to protons at C-2 and C-4 (δ7.32 and δ7.18) as a consequence of deshielding effect of the aryl groups attached to them. A singlet at δ9.87 was assigned to NH protons. The two singlets appeared at δ7.54 and 7.90 were attributed to NH_2 protons. The ^{13}C-NMR signals also confirmed the thiosemicarbazone structure as the chemical shifts **(TABLE-10)** are fully in agreement with the assigned structure. The assignments are also in consistent with the reported values of similar thiosemicarbazones[135]. A peak at δ180.86 was attributed to C=S carbon.

Based on the above spectral evidence, the product **SD_4** was characterised as *N^1-[1,5-bis(4-chlorophenyl)pent-1,4-dien-3-ylidene]thiosemicarbazide (13).*



(13)

Structure Elucidation of SD_{4A} (14)

It is an orange coloured needle shaped crystalline solid, m.p. 260°C and appears brown on exposure to iodine vapours (TLC). The structure of **SD_{4A}** has been elucidated by FT-IR, DCI-MS, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum (KBr) of **SD_{4A}** displayed characteristic bands at 3471, 3355 (NH), 2817 (C-H), 1584 (C=N), 1475 (Phenyl), 1351 (C=S), 1088 (C-N), 1007, 957, 829 and 774 cm^{-1}. The DCI-MS spectrum of **SD_{4A} (14) (FIG. 31)** showed a set of $[(M+1)]^+$ peak at m/z 376/378/380 (100.0/70.2/14.7), confirming its molecular weight 375/377/379 [$C_{18}H_{15}N_3Cl_2S$], which is equal to the sum of the molecular weights of compound **(8)** (302) and thiosemicarbazide (91) minus one molecule of water (18). This suggested that condensation of dienone **(8)** with thiosemicarbazide has occurred. A set of peaks at m/z 342/344/346 (6.3/4.2/1.2) $[(M+1)-H_2S]^+$ and an another set of peaks at m/z 316/318/320 (11.7/9.2/1.4) $[(M+1) - CSNH_2]^+$ observed in the spectrum are the common feature of exocyclic thiosemicarbazone moiety. The sets of peaks at m/z 211/213/215 (8.3/4.1/3.8) $[(M+1) - C_9H_8NCl]^+$ and

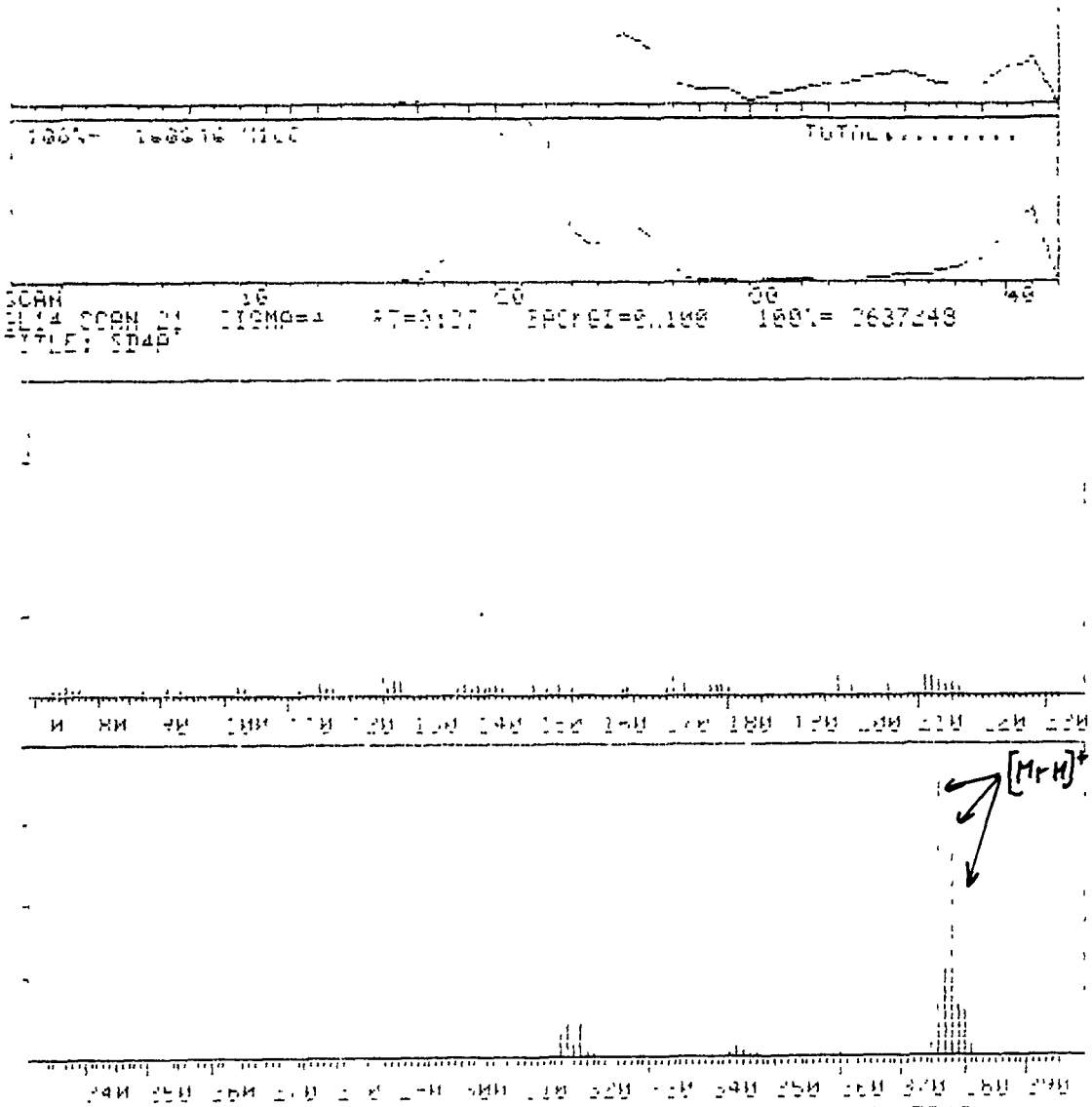


FIG. 31

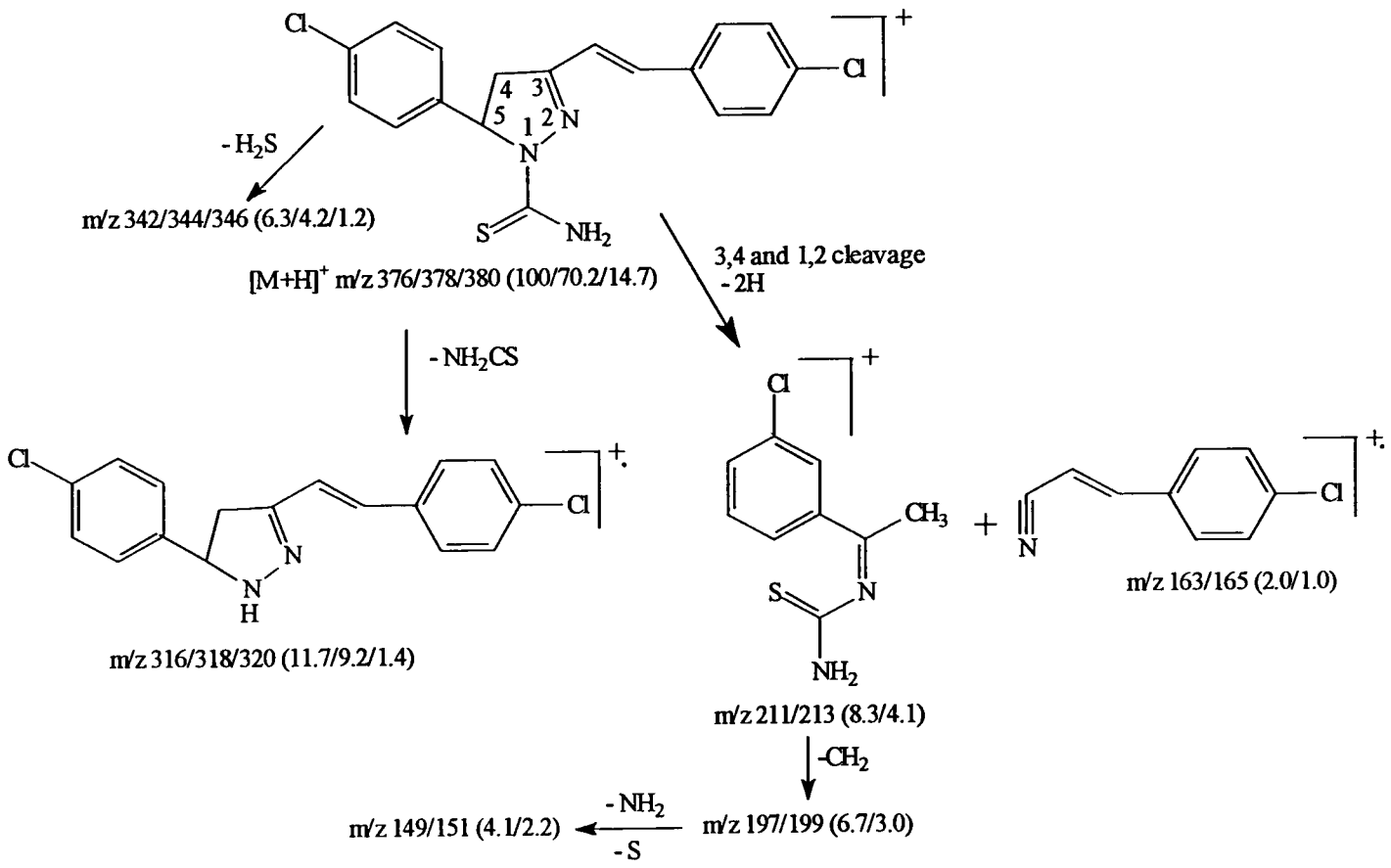

- H_2S
m/z 342/344/346 (6.3/4.2/1.2)
$[M+H]^+$ m/z 376/378/380 (100/70.2/14.7)
3,4 and 1,2 cleavage
- 2H
- NH_2CS
m/z 316/318/320 (11.7/9.2/1.4)
m/z 211/213 (8.3/4.1)
m/z 163/165 (2.0/1.0)
$-CH_2$
m/z 197/199 (6.7/3.0)
- NH_2
- S
m/z 149/151 (4.1/2.2)

CHART - 10

m/z 163/165/(2.0/1.0) [(M+1) - $C_9H_{10}N_2ClS]^+$ were obtained by the cleavage of 1-2 and 3-4 bonds of pyrazoline ring. The mode of fragmentations is shown in **CHART-10**. The ^{1}H-NMR (**FIG. 32**) and ^{13}C-NMR (**FIG. 33**) spectra of $\mathbf{SD_{4A}}$ dissolved in acetone-d_6 showed signals as assinged (**TABLE-11**). The assignments of all ^{1}H-NMR and ^{13}C-NMR signals to individual H- and C-atoms have been performed on the basis of typical chemical shift values, multiplicity, relative integrations and by a comparison with the spectra of the isomeric thiosemicarbazone (**13**). The ^{1}H-NMR spectrum of $\mathbf{SD_{4A}}$ revealed the presence of three double doublets as in $\mathbf{SD_5}$ represented by a typical ABX splitting pattern due to geminal and vicinal coupling of the two diastereotopic protons (megnetically non-equivalent methylene protons H_A, H_B) at C-4 and the methine proton (H_X) at C-5 of pyrazoline ring[132]. The two double doublets appeared at δ3.10 and δ3.84 with coupling constants J_{gem}=17.55 Hz, J_{vic}=3.81 Hz in the former and J_{gem}=17.55 Hz, J_{vic} = 11.60 Hz in the latter due to the coupling with axial proton at C-5, were assigned to equatorial and axial protons of C-4 respectively. The third double doublet at δ5.98 with coupling constants (J=3.81 Hz, J=11.60 Hz) due to vicinal coupling with two magnetically non equivalent protons of methylene group at C-4 of pyrazoline ring, was assigned to axial methine proton at C-5. The large coupling constants (J=11.60 Hz) of protons at C-4 and C-5 showed that they are trans oriented (diaxial, antiperiplanar) to each other. These signals are not present in the isomeric thiosemicarbazone (**13**). The two trans oriented doublets at δ7.09 (J=16.48 Hz) and δ7.15 (J=16.48 Hz) were attributed to ethylenic protons at C-1' and C-2' respectively. The coupling constant of ethylenic protons J=16.48 Hz indicated their trans geometry. In the ^{1}H-NMR spectrum of $\mathbf{SD_{4A}}$, there were two sets of ethylenic protons whereas in this case only one set of ethylenic protons

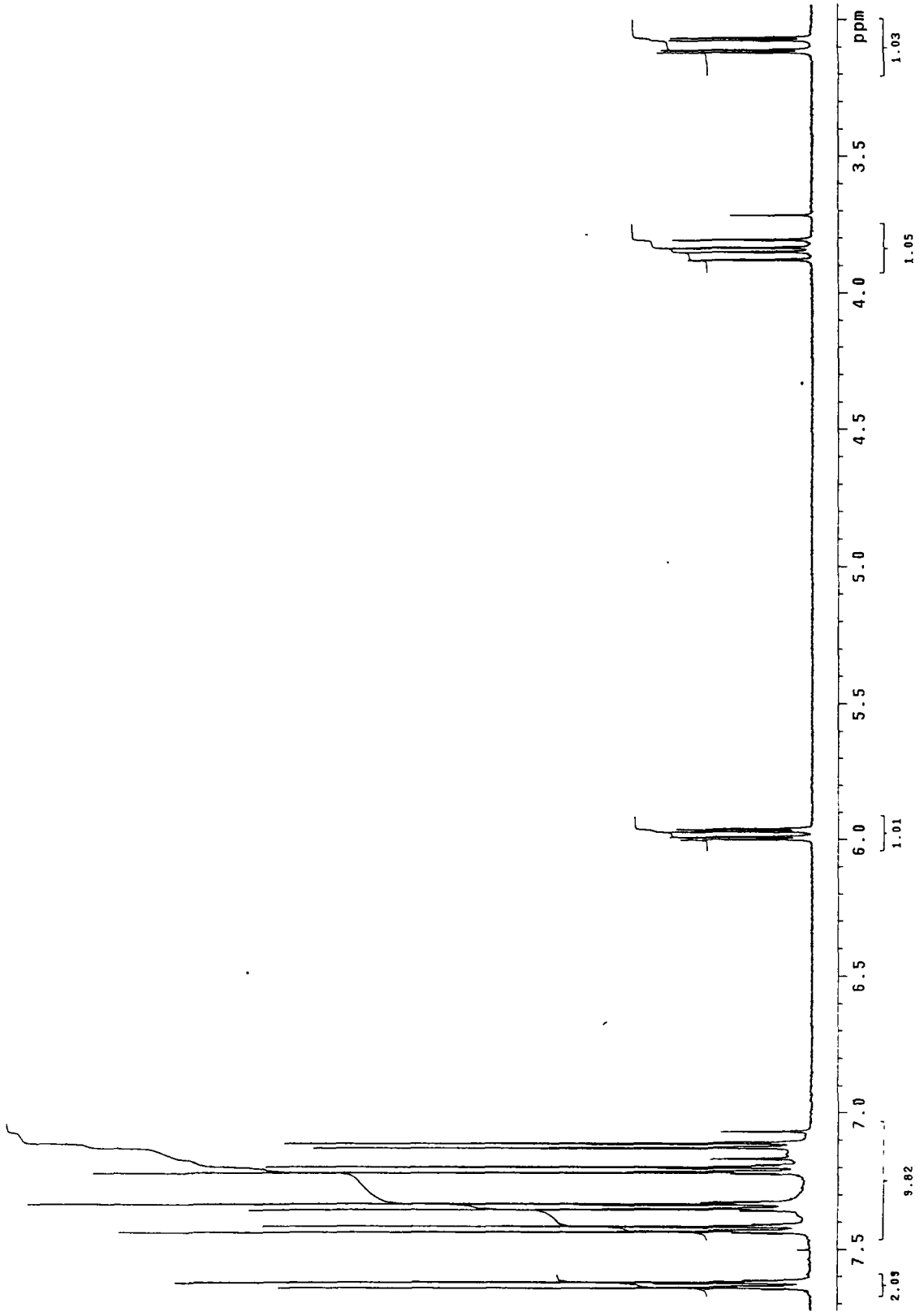

TOTALE INTEGRATIEWAARDE = 15.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
2.05
9.82
1.01
1.05
1.03

FIG. 32

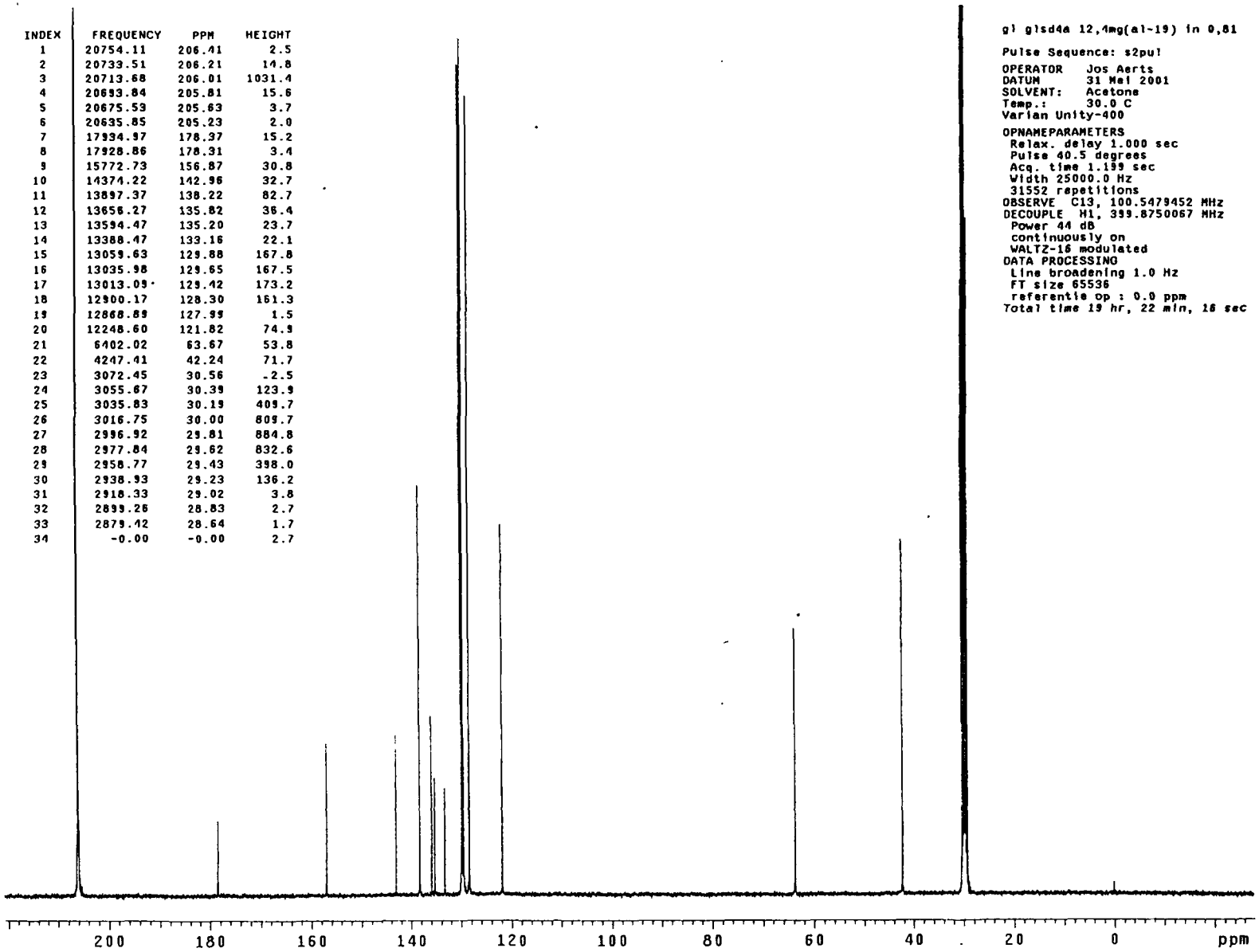

INDEX FREQUENCY PPM HEIGHT
1 20754.11 206.41 2.5
2 20733.51 206.21 14.8
3 20713.68 206.01 1031.4
4 20693.84 205.81 15.6
5 20675.59 205.63 3.7
6 20635.85 205.23 2.0
7 17934.97 178.37 15.2
8 17928.86 178.31 3.4
9 15772.73 156.87 30.8
10 14374.22 142.96 32.7
11 13897.37 138.22 82.7
12 13656.27 135.82 36.4
13 13594.47 135.20 23.7
14 13388.47 133.16 22.1
15 13059.63 129.88 167.8
16 13035.98 129.65 167.5
17 13013.09 129.42 173.2
18 12900.17 128.30 161.3
19 12868.89 127.99 1.5
20 12248.60 121.82 74.9
21 6402.02 63.67 53.8
22 4247.41 42.24 71.7
23 3072.45 30.56 -2.5
24 3055.67 30.39 123.9
25 3035.83 30.19 409.7
26 3016.75 30.00 809.7
27 2996.92 29.81 884.8
28 2977.84 29.62 832.6
29 2958.77 29.43 398.0
30 2938.93 29.23 136.2
31 2918.33 29.02 3.8
32 2899.26 28.83 2.7
33 2879.42 28.64 1.7
34 -0.00 -0.00 2.7
gl gisd4a 12,4mg(al-19) in 0,81
Pulse Sequence: s2pul
OPERATOR Jos Aerts
DATUM 31 Mei 2001
SOLVENT: Acetone
Temp.: 30.0 C
Varian Unity-400
OPNAMEPARAMETERS
Relax. delay 1.000 sec
Pulse 40.5 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
31552 repetitions
OBSERVE C13, 100.5479452 MHz
DECOUPLE H1, 399.8750067 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
referentie op : 0.0 ppm
Total time 19 hr, 22 min, 16 sec
200
180
160
140
120
100
80
60
40
20
0
ppm

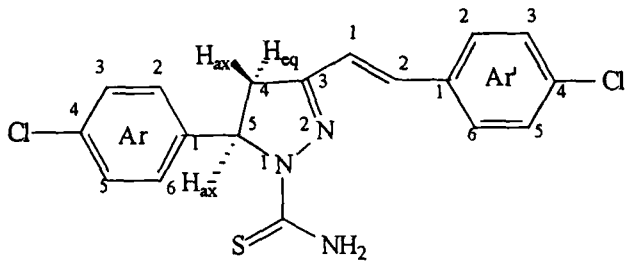
FIG. 33

TABLE -11 : ^{1}H-NMR and ^{13}C-NMR spectral data of SD_{4A} (14)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)	C-nr	δ (ppm)
1'	7.09	1H	d	$J_{1',2'}$=16.48	1'	121.82
2'	7.15	1H	d	$J_{1',2'}$=16.48	2'	138.22
4_{eq}	3.10	1H	dd	$J_{4eq,4ax}$=17.55, $J_{4eq,5ax}$=3.81	3	156.87
4_{ax}	3.84	1H	dd	$J_{4eq,4ax}$=17.55, $J_{4ax,5ax}$=11.60	4	42.24
5_{ax}	5.98	1H	dd	$J_{4eq,5ax}$=3.81, $J_{4ax,5ax}$=11.60	5	63.67
Ar-2,6	7.34	2H	d	$J_{Ar\text{-}2,6,\ Ar\text{-}3,5}$=8.55	Ar-1	142.96
Ar-3,5	7.21	2H	d	$J_{Ar\text{-}2,6,\ Ar\text{-}3,5}$=8.55	Ar-2,6	129.88
Ar'-2,6	7.63	2H	d	$J_{Ar'\text{-}2,6,\ Ar'\text{-}3,5}$=8.55	Ar-3,5	129.42
Ar'-3,5	7.43	2H	d	$J_{Ar'\text{-}2,6,\ Ar'\text{-}3,5}$=8.55	Ar-4	135.20
					Ar'-1	135.82
					Ar'-2,6	129.65
					Ar'-3,5	128.30
					Ar'-4	133.16
					> C = S	178.37

was observed due to the formation of pyrazoline ring. The aromatic protons signals appeared as two sets of A_2B_2 systems, one set at δ7.34 and δ7.21 (J=8.55 Hz) assigned to Ar-2,6 and Ar-3,5 protons and the other at δ7.63 and δ7.43 (J=8.55 Hz) to Ar'-2,6 and Ar'-3,5-protons. The ^{13}C-NMR spectrum of **SD_{4A}** showed signals which are in strong agreement with the formation of the ring. The *C*-3 signal at δ146.33 in the isomeric **SD_4** shifted to downfield at δ156.87 due to the formation of pyrazoline ring. The chemical shifts of other signals were found comparable with that of the isomeric thiosemicarbazone **SD_4**.

Based on these facts, the structure of **SD_{4A}** was formulated as *2-[3-{2-(4-chlorophenyl)ethenyl}-5-{(4-chlorophenyl)}-2-pyrazolin-1-yl]thiocarboxamide* ***(14)***.



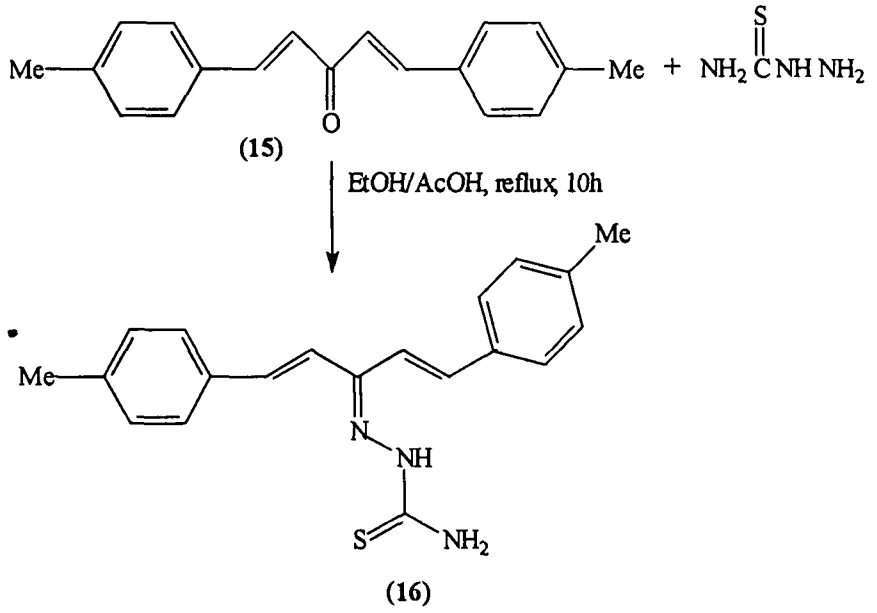
(14)

(iii) Reaction of 1,5-bis(4-methylphenyl)pent-1,4-dien-3-one (15) with thiosemicarbazide in the presence of acetic acid which yielded the thiosemicarbazone, N^1-[1,5-bis(4-methylphenyl)pent-1,4-dien-3-ylidene]thiosemicarbazide SD_2 (16) as the sole product. The desired product (pyrazoline) could not be obtained here.

A mixture of *1,5-bis(4-methylphenyl)pent-1,4-dien-3-one* (15) with thiosemicarbazide (molar ratio, 1:3) in ethanol in the presence of glacial acetic acid was refluxed for 10 h. TLC examination (silica gel 'G' benzene-ethyl acetate, 8:2 v/v) of reaction mixture showed the formation of only one

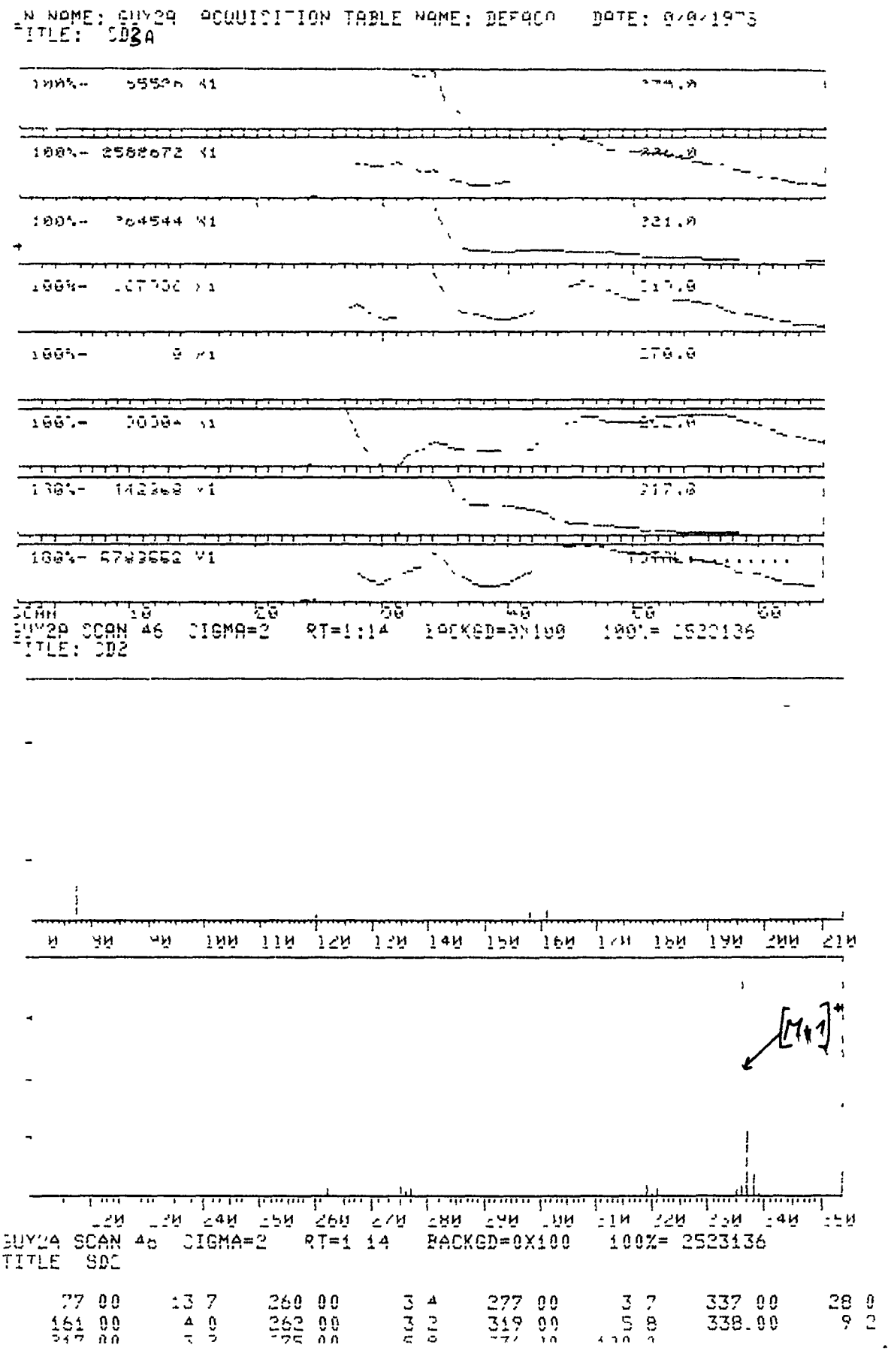
component labelled as SD_2. It was purified by column chromatography over silica gel using benzene-ethylacetate (8:2 v/v) as eluent followed by crystallization to give SD_2 (16) as orange crystalline needles in 65% yield.

The reaction sequence is given below :



Structure Elucidation of SD_2 (16)

It is an orange crystalline needle, m.p. 160 °C and appears brown on exposure to iodine vapours (TLC). The constitution of SD_2 has been established by FT-IR, DCI-MS, ^{1}H-NMR and ^{13}C-NMR spectra and also by a comparison with the spectra of SD_4. The DCI-MS (NH_3 as reagent gas) spectrum (**FIG. 34**) of SD_2 showed a peak at m/z 336 (100), corresponding with $[M+1]^+$ $[C_{20}H_{21}N_3S]$, confirming its molecular weight (335) which is equal to the sum of the molecular weights of *1,5-bis (4-methylphenyl)pent-1,4-dien-3-one* (**14**) (262) and thiosemicarbazide (91) minus one molecule of water (18). This indicated that the formation of thiosemicarbazone has occurred by the condensation of the dienone (**14**) with thiosemicarbazide. The


N NAME: GUY29 ACQUISITION TABLE NAME: DEFAC0 DATE: 0/0/1973
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SCAN
GUY29 SCAN 46 SIGMA=2 RT=1:14 BACKGD=0X100 100%= 2523136
TITLE: CD2
[M+1]+
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TITLE SDC
77 00 13 7 260 00 3 4 277 00 3 7 337 00 28 0
161 00 4 0 262 00 3 2 319 00 5 8 338.00 9 2

FIG. 34

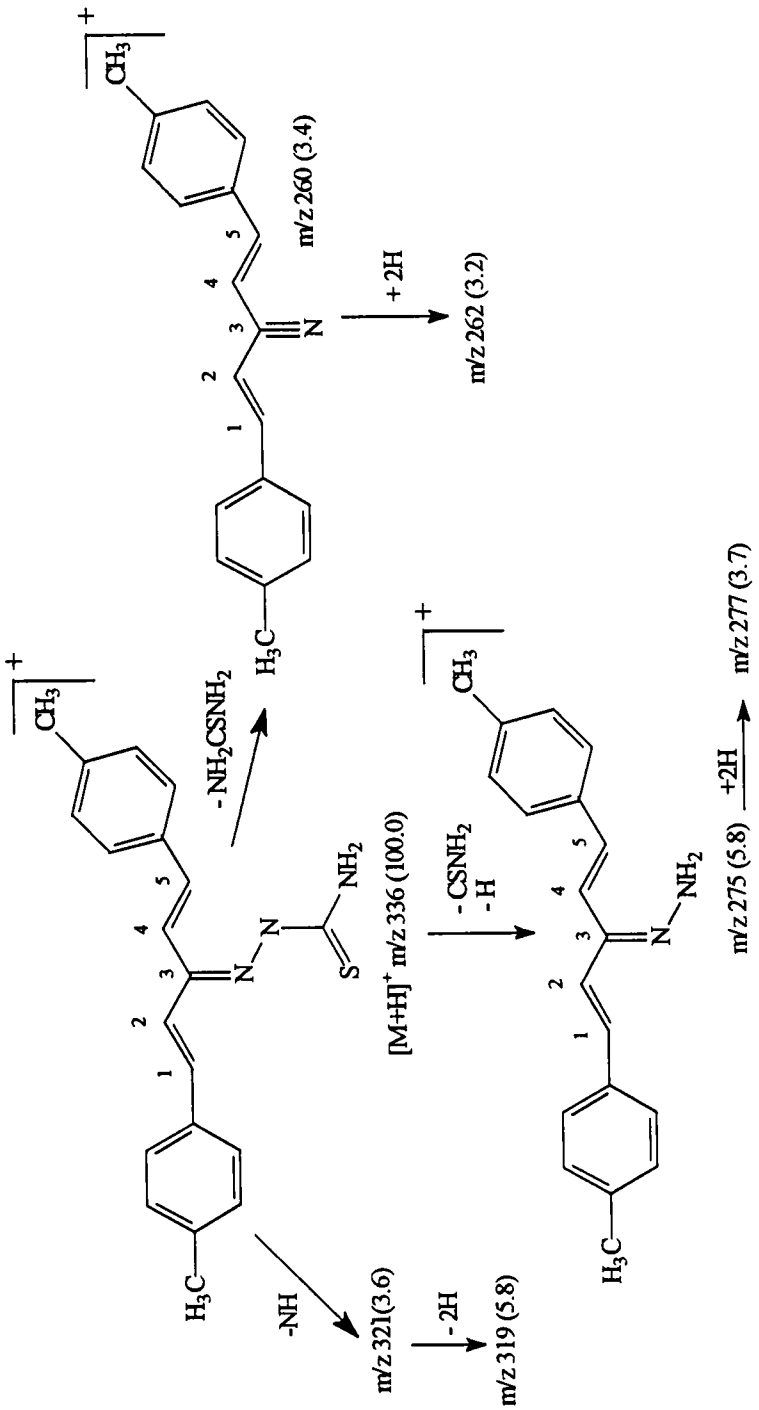

m/z 260 (3.4)
+2H
m/z 262 (3.2)
-NH2CSNH2
[M+H]+ m/z 336 (100.0)
-CSNH2
-H
-NH
m/z 321(3.6)
-2H
m/z 319 (5.8)
m/z 275 (5.8)
+2H
m/z 277 (3.7)

CHART - 11

mass fragmentation pattern was found to be similar to that of **SD_4**. A peak at m/z 319 was arised by the loss of ammonia molecule from molecular ion $[(M+1)-NH_3]^+$. The corresponding $[(M+1)-CSNH_2]^+$ peak was observed at m/z 276 by the cleavage of N-C bond of the thiocarboxamide moiety. A characteristic peak for thiosemicarbazone moiety appeared at m/z 262 $[(M+1)-NHCS\ NH]^+$. The mode of fragmentations is showed in **CHART-11**. The ^{1}H-NMR **(FIG. 35)** and ^{13}C-NMR **(FIG. 36)** spectra of **SD_2** dissolved in acetone-d_6 showed signals as assigned in **TABLE-12**. The assignments of all ^{1}H-NMR and ^{13}C-NMR signals to individual H- and C-atoms have been performed on the basis of typical chemical shift values, multiplicity, relative integrations and by a comparison with the ^{1}H-NMR and ^{13}C-NMR spectra of previously established compound **SD_4 (13)**. The ^{1}H-NMR spectrum of **SD_{2A}** showed two doublets at δ7.23 and δ7.31 with large coupling constants (J=16.02Hz) assigned to protons at C-2 andC-1 and other two doublets at δ7.08 and δ7.30 with coupling constants (J=16.00 Hz) attributed to protons at C-4 and C-5 respectively. The large coupling constant (J=16.02 Hz) of vicinal protons confirmed their trans disposition. The protons at C-1 and C-5 appeared at lower field (δ7.31 and δ7.30) as compared to protons at C-2 and C-4 (δ7.23 and δ7.08) as a consequence of deshielding effect of the aryl groups attached to them. A singlet at δ9.80 was assigned to NH proton. The two singlets appeared at δ7.53 and δ7.86 were attributed to NH_2 protons. The ^{1}H-NMR spectrum also showed significant aromatic proton peaks in the form of A_2B_2 pattern at δ7.62 and δ7.24 as two doublets with J=8.08 Hz each for Ar-2,6, Ar-3,5 and another two doublets at δ 7.49 and δ7.20 with J=8.24 Hz corresponding to Ar'-2,6 and Ar'-3,5 respectively. The ^{13}C-NMR signals of **SD_2 (TABLE-12)** were also found comparable with that of **SD_4 (13) TABLE-10**. The ^{13}C-NMR signals were fully in agreement with the assigned

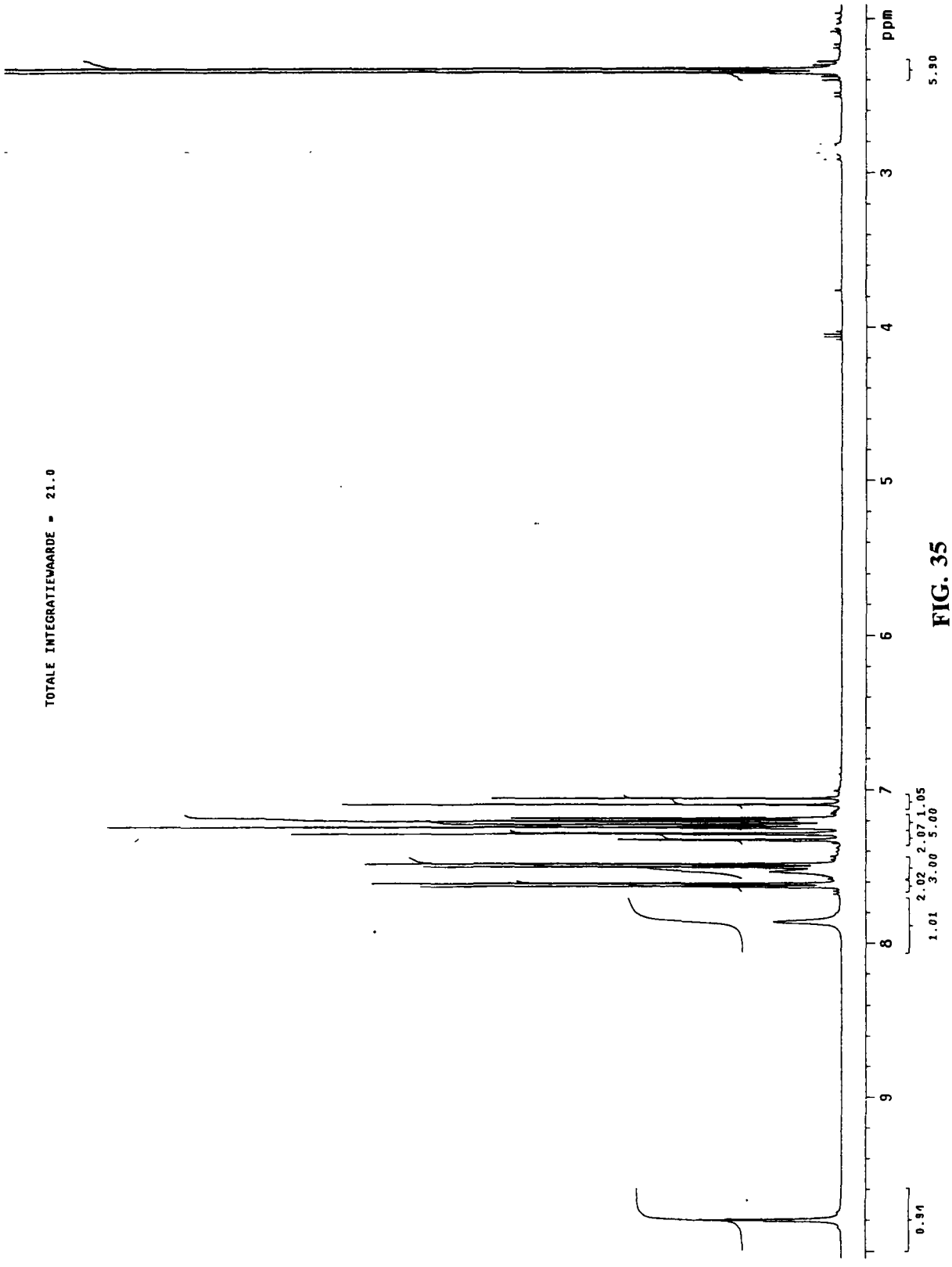
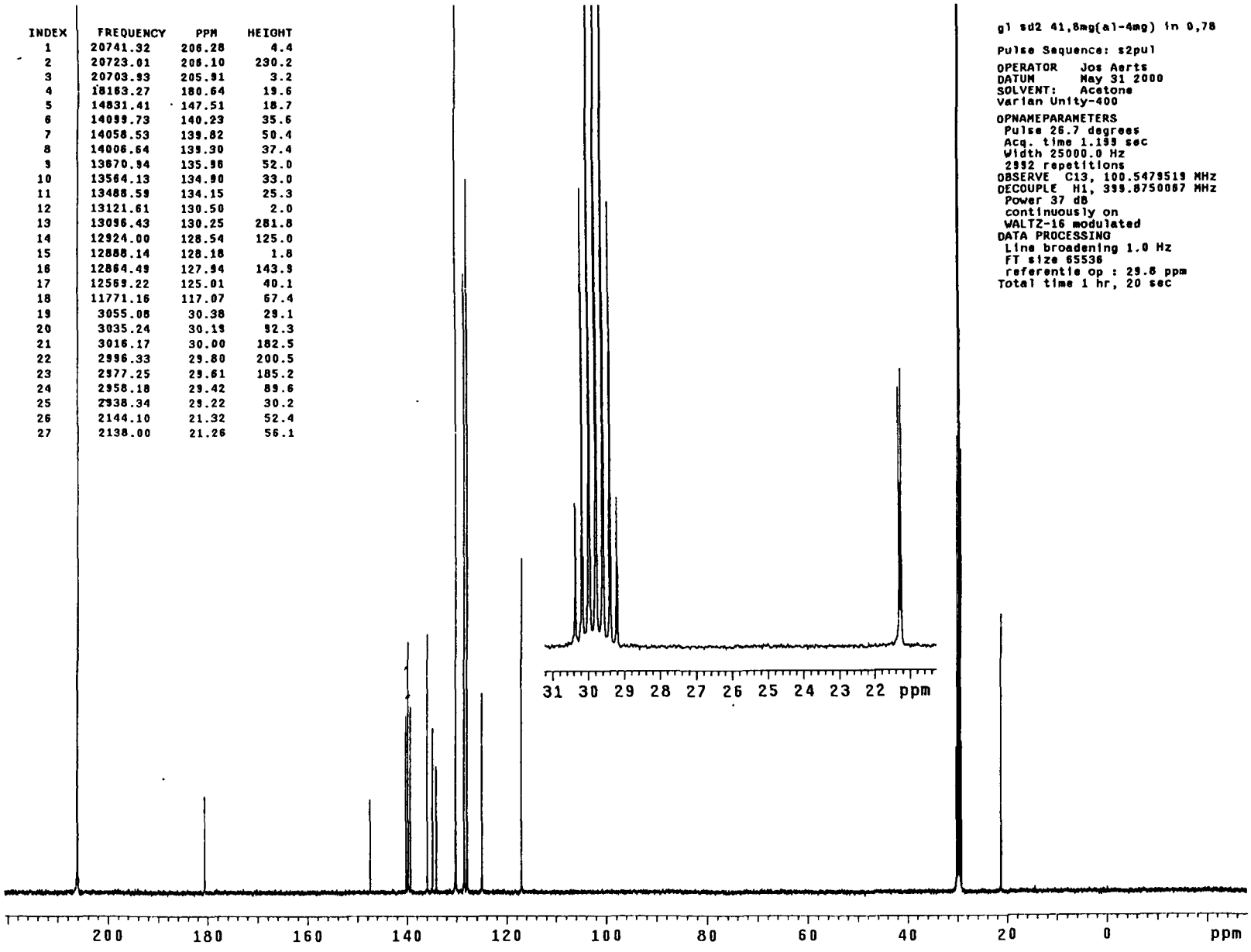


FIG. 35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5 14831.41 147.51 18.7
6 14099.73 140.23 35.6
7 14058.53 139.82 50.4
8 14006.64 139.30 37.4
9 13870.94 135.96 52.0
10 13564.13 134.90 33.0
11 13488.59 134.15 25.3
12 13121.61 130.50 2.0
13 13096.43 130.25 281.8
14 12924.00 128.54 125.0
15 12888.14 128.18 1.8
16 12864.49 127.94 143.9
17 12569.22 125.01 40.1
18 11771.16 117.07 67.4
19 3055.08 30.38 29.1
20 3035.24 30.19 92.3
21 3016.17 30.00 182.5
22 2996.33 29.80 200.5
23 2977.25 29.61 185.2
24 2958.18 29.42 89.6
25 2938.34 29.22 30.2
26 2144.10 21.32 52.4
27 2138.00 21.26 56.1
g1 sd2 41,8mg(a1-4mg) in 0,78
Pulse Sequence: s2pul
OPERATOR Jos Aerts
DATUM May 31 2000
SOLVENT: Acetone
Varian Unity-400
OPNAMEPARAMETERS
Pulse 26.7 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
2992 repetitions
OBSERVE C13, 100.5479519 MHz
DECOUPLE H1, 399.8750087 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
referentie op : 29.8 ppm
Total time 1 hr, 20 sec
31 30 29 28 27 26 25 24 23 22 ppm
200 180 160 140 120 100 80 60 40 20 0 ppm

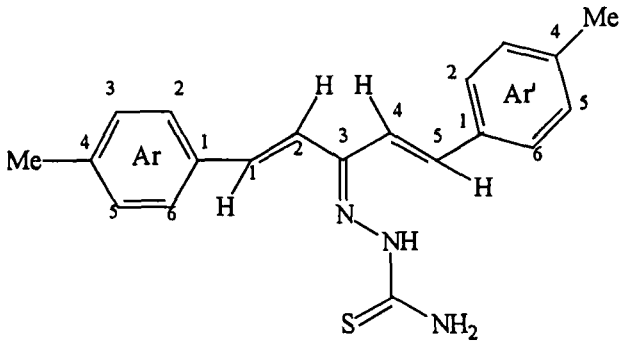
FIG. 36

TABLE -12 : ^{1}H-NMR and ^{13}C-NMR spectral data of SD_2 (16)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)	C-nr	δ (ppm)
1	7.31	1H	d	$J_{1,2}$=16.02	1	139.82
2	7.23	1H	d	$J_{1,2}$=16.02	2	125.01
4	7.08	1H	d	$J_{4,5}$=16.00	3	147.51
5	7.30	1H	d	$J_{4,5}$=16.00	4	117.07
NH	9.80	1H	s	–	5	135.96
NH_2	7.53, 7.86	2H	s	–	Ar-CH_3	21.32
Ar-CH_3	2.35	3H	s	–	Ar'-CH_3	21.26
Ar'-CH_3	2.33	3H	s	–	Ar-2,6	128.54
Ar-2,6	7.62	2H	d	$J_{Ar\text{-}2,6}$=8.08	Ar-3,5	130.25
Ar-3,5	7.24	2H	d	$J_{Ar\text{-}2,6}$=8.08	Ar-1	134.90
Ar'-2,6	7.49	2H	d	$J_{Ar'\text{-}2,6}$=8.24	Ar-4	140.23
Ar'-3,5	7.20	2H	d	$J_{Ar'\text{-}2,6}$=8.24	Ar'-1	134.15
					Ar'-2,6	127.94
					Ar'-3,5	130.23
					Ar'-4	139.30
					> C=S	180.64

structure. These assignments were also in consistent with the reported values of similar thiosemicarbazones[135]. A peak at δ180.64 was attributed to C=S carbon. The methyl carbons appeared at δ21.26 (C-Ar'-CH_3) and 21.32 (C-Ar-CH_3). The ring carbons were observed at δ128.54 (C-Ar-2,6), 130.25 (C-Ar-3,5), 134.90 (C-Ar-1), 140.23 (C-Ar-4) and δ127.94 (C-Ar'-2,6), 130.23 (C-Ar'-3,5) 134.15 (C-Ar'-1), 139.30 (C-Ar'-4).

On the basis of the above facts the product **SD_2** was characterized as *N^1-[1,5-bis(4-methylphenyl)pent-1,4-dien-3-ylidene]thiosemicarbazide* ***(16)***.



(16)

Experimental

EXPERIMENTAL

1,5-Bis(3,4-dimethoxyphenyl)pent-1,4-dien-3-one (4)

The compound (4) was prepared exactly as described in **CHAPTER-1.**

2-[3-{3,4-Dimethoxyphenyl)ethenyl}-5-{3,4-dimethoxyphenyl)}-2-pyrazolin-1-yl]thiocarboxamide SD_{5A} (12)

A mixture of 1,5-bis(3,4-dimethoxyphenyl)pent-1,4-dien-3-one (4) (950 mg, 2.68 mmol) and thiosemicarbazide (732 mg 8.05 mmol) in ethanol in presence of a few drops of conc. HCl was refluxed with stirring at 80 °C on an oil bath for 10 h. The reaction mixture on TLC examination (silica gel 'G', benzene-ethyl acetate, 8:2 v/v) showed two spots, one very minor (upper) and the other major (lower) labelled as SD_{5A}. The residue was subjected to column chromatography over silica gel using benzene-ethyl acetate (8:2 v/v) as eluent. Elution first furnished the orange coloured showed as minor-product, R_f 0.60 (benzene-ethyl acetate, 8:2 v/v), dark brown on TLC (I_2). Further elution yielded a dark-brown solid which on crystallization (benzene-acetone) furnished SD_{5A} (12) as brown crystalline needles 1049 mg (65%), m.p. 130 °C, R_f 0.48 (benzene-ethyl acetate, 8:2 v/v).

Spectral data of (12)

IR (KBr pellet) : υ_{max} cm^{-1} 3447, 3338 (NH), 2934, 2834 (C-H), 1659 (C=C), 1589 (C=N), 1513, 1465 (phenyl), 1345 (C=S), 1261, 1136 (-C-O-C), 1020 (C-N), 961, 805, 759, 612, 575.

^{1}H-NMR (acetone-d_6, 400 MHz) : δ_H 7.01 (1H, d, J=16.48Hz, H-1'), 7.04 (1H, d, J=16.48 Hz, H-2'), 3.08 (1H, dd, J=17.55 Hz, J=3.21 Hz, H-4_{eq}), 3.76(1H, dd, J=17.55 Hz, J=11.29 Hz, H-4_{ax}), 5.91 (1H, dd, J=3.21

Hz,J=11.29 Hz, H-5_{ax}), 3.76-3.88 (12H, s, 4 x OCH_3), 6.84 (1H, d, J=2.14Hz, H-Ar-2), 6.86 (1H, d, J=8.24 Hz H-Ar-5), 6.69(1H, dd, J=2.14 Hz, J=8.24 Hz, H-Ar-6), 7.26 (1H, d, J=2.14 Hz, H-Ar'-2), 6.96 (1H, d, J=8.24 Hz, H-Ar'-5), 7.12 (1H, dd, J=2.14 Hz, J=8.24 Hz, H-Ar'-6).

^{13}C-NMR (acetone-d_6, 100 MHz) : δ_C 122.24 (C-1'), 139.72 (C-2'), 157.66 (C-3), 42.42 (C-4), 63.78(C-5), 178.08 (C=S), 56.25(4 x OCH_3), 136.69(C-Ar-1), 111.31 (C-Ar-2), 151.79 (C-Ar-3), 150.52 (C-Ar-4), 113.90 (C-Ar-5), 118.92 (C-Ar-6), 129.97 (C-Ar'-1), 110.88 (C-Ar'-2), 150.77 (C-Ar'-3), 149.69 (C-Ar'-4), 112.81 (C-Ar'-5), 118.49 (C-Ar'-6).

DCI-MS (NH_3) : m/z 430(10.7), 429(34.3), 428(100.0), 427(6.8), 426(3.0), 414(4.4), 412(2.4), 398(2.2), 397(7.4), 396(2.4), 395(2.0), 394(6.3), 370(2.2), 369(10.7), 368(7.7), 367 (13.3), 355(2.2), 354(2.0), 353(2.2), 352(5.1), 351(7.3), 238 (4.0), 237(6.4), 224 (2.0), 223(11.5), 203(6.7), 189 (4.0), 165(4.0), 164(4.2), 163(4.6), 153(3.2), 153(2.4), 151(7.3), 79(2.2), 78(2.2), 77(4), 76(2.2).

1,5-Bis(4-chlorophenyl)pent-1,4-dien-3-one (8)

The compound **(8)** was prepared exactly as described in **CHAPTER-1.**

2-[3-{2-(4-Chlorophenyl)ethenyl}-5-{(4-chlorophenyl)}-2-pyrazolin-1-yl]thiocarboxamide SD_{4A} (14) and N^1-[1,5-bis(4-chlorophenyl) pent-1,4-dien-3-ylidene]thiosemicarbazide SD_4 (13)

A mixture of 1,5-bis(4-chlorophenyl)pent-1,4-dien-3-one **(8)** (680 mg 2.25 mmol) and thiosemicarbazide (614 mg, 6.75 mmol) in presence of a few drops of conc. HCl in ethanol (25 ml) was refluxed with stirring at 80 °C on an oil bath for 10 h. The progress of the reaction was monitored by TLC at every 30 minutes. After completion, the reaction mixture was concentrated under reduced pressure, extracted with ethyl acetate and washed with water

several times until the solution was neutral. The ethyl acetate solution was then dried over Na_2SO_4. The solvent was evaporated and the orange-coloured oily residue left was examined by TLC (silica gel 'G', benzene-ethyl acetate, 8:2 v/v). It was found to be a mixture of two components, one minor (upper) and the other major (lower), labelled as **SD_4** and **SD_{4A}**. The oily residue was chromatographed over silica gel column using benzene-ethyl acetate, 8:2 v/v as an eluent. Elution of the column first furnished an orange coloured solid which on crystallization from benzene-acetone yielded **SD_4 (13)** as light orange crystalline globules, 123 mg (10%), m.p. 130 °C, R_f 0.62 (benzene-ethyl acetate, 8:2 v/v).

Spectral data of SD_4 (13)

IR (KBr pellet) : υ_{max} cm^{-1} 3423, 3247 (NH) 1595 (C=N), 1595, 1497 (phenyl), 1197 (C=S), 1086 (C–N), 1008 , 957, 812, 708 (C–Cl), 623, 520, 480.

^{1}H-NMR (acetone-d_6, 400 MHz) : δ_H 7.77 (2H, d, J=8.55Hz, H-Ar-2,6); 7.46 (2H, d, J=8.55Hz, H-Ar-3,5), 7.64 (2H, d, J=8.40Hz, H-Ar'-2,6), 7.41 (2H, d, J=8.40Hz, H-Ar'-3,5), 7.46 (1H, d, J=16.48Hz, H-1), 7.32 (1H, d, J=16.48Hz, H-2), 7.18 (1H, d, J=16.17Hz, H-4), 7.38 (1H, d, J=16.17Hz, H-5), 7.54, 7.90 (1H, s, NH_2), 9.87 (1H, s, NH)

^{13}C-NMR (acetone-d_6, 100 MHz,) : δ_C 138.37 (C-1), 126.54 (C-2), 146.33 (C-3), 118.88 (C-4), 134.46 (C-5), 129.50-136.54 (Ar+Ar'), 180.86 (C=S)

DCI-MS (NH_3) : m/z 376/378/380 [(M+1)/(M+3)/(M+5), 100/67.1/13.6], 375 (7.0), 346 (1.6), 344 (4.5), 342 (7.0); 321(7.5); 320(11.6), 319(51.0); 318(30.8); 317(95.9), 316(28.7), 315(30.3), 306(1.5); 304(6.5); 302(13.6); 300(5.5), 217(2.0), 216(3.2); 215(4.5), 214(2.2), 213(4.4), 212(5.5),

211(8.0), 207(2.2), 205(5.0), 203(1.6), 202(2.0), 199(2.2), 198(1.2), 197(5.0); 180(2.0), 179(2.6), 178(2.8); 177(2.2), 176(2.0), 173(2.4); 172(1.4); 171(6.5); 166(1.6); 165(1.8); 164(2.1); 163(2); 155(1.8); 154(1.7); 153(1.6); 152(1.5); 151(2.0); 150(1.9); 149(5.5); 144(2.2); 142(4.2); 140(6.0); 139(4); 138(5.0); 137(3.8); 136(2.4); 128(4.5), 127(5.5); 126(2.2); 125(10.6); 117(3.4); 116(3.6), 115(7.0); 103(2.2); 102(7.0); 101(2.4); 94(1.4); 93(2.2), 92(1.6); 91(3); 89(4.2); 78(2.2); 77(10.6); 76(7.5); 75(3.4); 74(3.2); 73(2).

Further elution of the column yielded a dark brown solid which on crystallization from benzene-acetone afforded **SD_{4A}** as brown needles shaped crystalline solid 740 mg (59.96%), m.p. 260 °C, R_f 0.58 (benzene : ethyl acetate, 8:2 v/v).

Spectral data of SD_{4A} (14)

IR (KBr pellet) : υ_{max} cm^{-1} 3471. 3355 (NH), 2817 (C-H) 1584 (C=N), 1584, 1475.(phenyl) 1351 (C=S), 1088 (C-N), 1007, 957, 829, 774, 671 cm^{-1}.

^{1}H-NMR (acetone-d_6, 400 MHz) : δ_H : 7.09 (1H, d, J=16.48Hz, H-1'), 7.15 (1H, d, J=16.48Hz, H-2'), 3.10 (1H, dd, J=17.55Hz, J=3.81, H-4_{eq}), 3.84 (1H, dd, J=17.55Hz, J=11.60Hz, H-4_{ax}), 5.98 (1H, dd, J=3.81Hz, J=11.60Hz, H-5_{ax}). 7.34(2H, d, J=8.55Hz, H-Ar-2,6), 7.21(2H, d, J=8.55Hz, H-Ar-3,5), 7.63 (2H, d, J=8.55Hz, H-Ar'-2,6), 7.43 (2H, d, J=8.55Hz, H-Ar'-3,5).

^{13}C-NMR (acetone-d_6, 100MHz) : δ_C 121.82(C-1'), 138.22 (C-2'), 156.87 (C-3). 42.24 (C-4) 63.67 (C-5), 142.96 (C-Ar-1), 129.88 (C-Ar-2,6), 129.42 (C-Ar-3,5); 135.20 (C-Ar-4), 135.82 (C-Ar'-1), 129.65 (C-Ar'-2,6), 128.30 (C-Ar'-3,5); 133.16 (C-Ar'-4), 178.37 (C=S)

DCI-MS (NH_3) : m/z 376/378/380 [(M+1)/(M+3)/(M+5)/100/70.2/14.7],

375/377/379 (8.7/28.1/16.0), 346 (1.2), 345(1.8), 344(4.2), 343 (1.6), 342(6.3), 321(1.0), 320(1.4), 319(11.0), 318(9.2), 317(21.3), 316(11.7), 315(9.6), 217(10), 216(2.2), 215 (3.8), 214(3.2), 213(4.1), 212(8.6), 211(8.3), 207 (1.8), 205(3.8), 203(1.0), 202(1.1), 199(3), 198(1.8), 197(6.7), 182(1.8), 181(1.8), 180(2), 179(2.2), 178(4.2), 177(3.6), 176(2.1), 175(2.0), 173(3.6), 172(2.2), 171(8.2), 170(4.2), 165(1.0), 163(2.0), 155(3.2), 153(4), 151(2.2), 149(4.1), 144(2.2), 143(3), 142(2.0), 141(2.1), 140(3.6), 139(3.4), 138(3.4), 137(1), 129(1.6), 127(4.2), 125(6.1), 117(2.0), 116(2.2), 115(4.7), 103(2.2), 102(2.4), 101(1.4), 93(2.0), 91(2.4), 89(3), 77(2), 76(1.8), 75(3.8), 74(2.1), 73(2).

1,5-Bis(4-methylphenyl)pent-1,4-dien-3-one (15)

It was prepared as described in **(4)/(8)** above by condensing acetone with *p*-tolualdehyde (commercially available). A mixture of *p*-tolualdehyde (5 gm, 0.042 mol) and acetone (1.2 gm, 0.021 mol) in ethanol (20 ml) was kept on an ice bath and to this was added sodium hydroxide (4.17 gm, 0.104 mol) dropwise with stirring. A flocculent precipitate was formed during addition. It was stirred further for 1 h and then worked up as usual. The yellow solid thus obtained was recrystallized from benzene to give **(15)** as light yellow crystalline needles, 4.30 gm (71.27%), m.p. 175 °C, R_f 0.52 (pet. ether-EtOAc, 8:2 v/v)

Spectral data of (15)

^{1}H-NMR (acetone-d_6, 400 MHz) : δ_H 7.24 (2 x 1H, d, J=16.17, H-2, H-4), 7.75 (2 x 1H, d, J=16.17, H-1, H-5), 7.27 (2 x 2H, d, J=8.85, 2 x Ar-3,5), 7.64 (2 x 2H, d, J=8.85, 2 x Ar-2,6), 2.05 (6H, s, 2 x Ar-CH_3).

^{13}C-NMR (acetone-d_6, 100 MHz) : δ_C 21.42 (C-Ar-CH_3); 125.80 (C-2/C-4),

143.20 (C-1/C-5), 133.45 (2 x C - Ar - 1), 129.28 (2 x C-Ar-2,6),130.51 (2 x C-Ar-3,5), 141.53 (2 x C-Ar-4), 188.87 (C=O).

DCI-Mass (NH_3) : m/z 263 (100.0), 264 (23.9), 265 (3.3), 262 (3.1), 145 (4.6).

N^1-[1,5-Bis(4-methylphenyl)pent-1,4-dien-3-ylidene]thiosemicarbazide SD_2 (16)

A mixture of 1,5-bis(4-methyl phenyl)pent-1,4-dien-3-one (600 mg, 2.2 mmol) and thiosemicarbazide (625 mg, 6.87 mmol) in ethanol in the presence of glacial acetic acid (2 ml) was refluxed with stirring at 80°C on an oil bath for 10 h. Monitoring the progress of reaction by TLC (silica gel 'G', benzene-ethyl acetate, 8:2 v/v) revealed the presence of a single spot, labelled as SD_2. The reaction mixture was worked up as above and the yellow solid thus obtained was crystallized (benzene-acetone) to give **(16)** as an orange crystalline needles, 771 mg, (65%), m.p. 160°C, R_f 0.52 (pet. ether-ethyl acetate, 8:2 v/v).

Spectral data of (16)

^{1}H-NMR (acetone-d_6, 400 MHz) : δ_H 7.31 (1H, d, J=16.02 Hz, H-1), 7.23 (1H, d, J=16.02 Hz, H-2), 7.08 (1H, d, J=16.0 Hz, H-4), 7.30 (1H, d, J=16.0 Hz, H-5), 2.35(3H, s, H-Ar-CH_3), 2.33 (3H, s, H-Ar'-CH_3), 7.62(2H,d, J=8.08Hz, H-Ar-2,6), 7.24(2H, d, J=8.08Hz, H-Ar-3,5), 7.49 (2H, d, J=8.24Hz, H-Ar'-2,6), 7.20(2H, d, J-8.24Hz, H-Ar'-3,5), 7.53, 7.86(2H, s, NH_2), 9.80(1H, s, NH).

^{13}C-NMR (acetone-d_6, 100 MHz) : δ_C 139.82 (C-1), 125.01(C-2), 147.51(C-3), 117.07(C-4), 135.96 (C-5), 180.64(C=S), 21.32(C-Ar-CH_3), 21.26(C-Ar'-CH_3), 128.54(C-Ar-2,6), 130.25(C-Ar,3,5), 134.90(C-Ar-1),

140.23(C-Ar-4), 134.15(C-Ar'-1), 127.94(C-Ar'-2,6), 130.23(C-Ar'-3,5), 139.30(C-Ar'-4).

DCI-MS (NH_3) : m/z 338(9.2), 337(28.0), 336(100), 335(2.6), 321(3.6), 319(5.8), 277(3.7), 276(2.0), 275(5.8), 262(3.2), 260(3.4), 217(3.2), 192(1.8), 191(1.5), 185(2.4), 177(2.8), 162(2.0), 161(4.0), 160(3.8), 151(1.8), 135(1.2), 134(1.4), 133(2.0), 132(1.9), 120(2.0), 119(1.4), 118(1.5), 117(1.6), 116(1.9), 115(1.8), 106(2.2), 105(2.0), 78(1.8), 77(13.7), 76(1.0).

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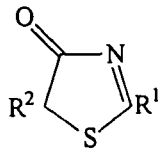
Chapter - 3

2-[3,5-Di-aryl substituted-2-Pyrazolinyl]Thiazolin-4-ones from Chalcones

Theoretical

THEORETICAL

Thiazolin-4-ones belong to an important class of biologically active five membered heterocyclic compounds with a nitrogen and a sulphur atom at 1,3-positions and a double bond in the ring.



(I)

$R^1 = R^2 = NR_2 = alkyl = aryl$

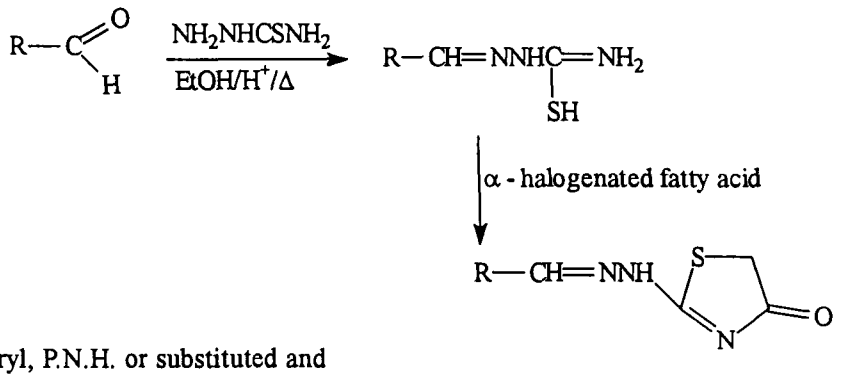
The compounds containing thiazolinone moiety are associated with diverse biological activities and are found to be very potent against a number of diseases[1-3] such as antiulcer and cytoprotective[4], antimicrobial[5-6], antiallergic[7-8], antiinflammatory[9], antitubercular[10], antiproliferative[11], antibone disorder[12], anti AIDS[13], cardiotonics[14-16], diabetes[17], fungicidal[18], herbicidal[19], fibrinogen receptor[20], insecticidal[21] activity. Thiosemicarbazones of various aldehydes and ketones have been found to posses broad spectrum of medicinal properties[22].

N.N. Khovratovich *et al.*[22] have reported the synthesis of 2-amino-4-thiazolinone **(II)** and its derivatives. The spectral studies showed that in crystalline state it has an imino **(II)** and in solution an amino structure **(III)**.

(II) (III)

BUU-HOI *et al.*[24-26] have synthesized a number of thiosemicarbazones and their corresponding extra nuclear 4-oxo-Δ^2-thiazolin-2-yl-hydrazones by

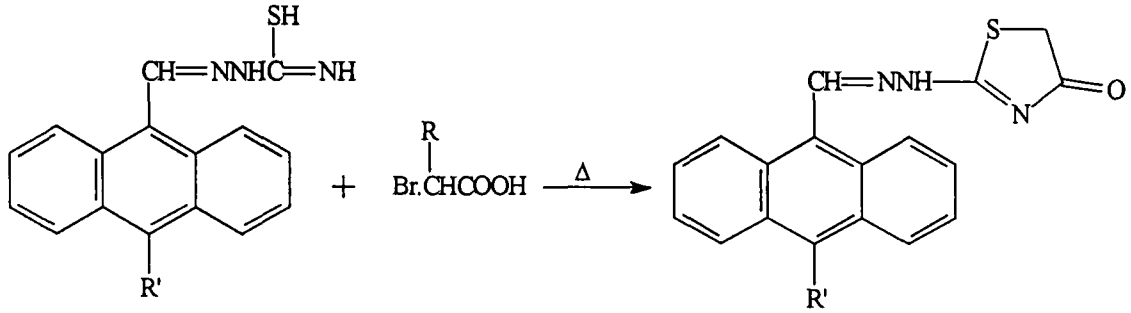
heating various aldehydes and ketones with thiosemicarbazide in dry ethanol in acidic medium followed by cyclocondensation of thiosemicarbazones formed with α-halogenated fatty acids to the corresponding 4-keto-2-thiazolinyl hydrazones of the general formula.



R =alkyl aryl, P.N.H. or substituted and unsubstituted heterocyclic group.

(IV)

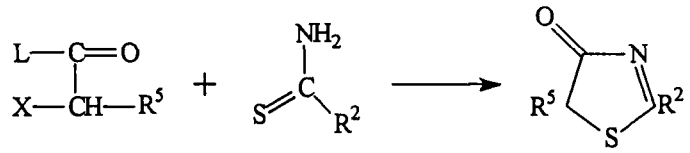
BUU-HOI also reported a number of 4-oxo-Δ^2-thiazolin-2-yl-hydrazones (V) of aldehydes and ketones by heating a mixture of thiosemicarbazones and chloroacetic acid or the appropriate α-bromo-acid with sodium acetate. The synthesized compounds were found to be highly active *in vitro* against *Mycobaterium tuberculosis* and some of these also showed antiviral properties towards DNA and RNA viruses in tissue cultures.



R = H
R' = H, alkyl

(V)

2-substituted Δ^2-thiazolin-4-ones[27] (**VI**) were reported by condensing α-haloacids and their derivatives with thioamides.

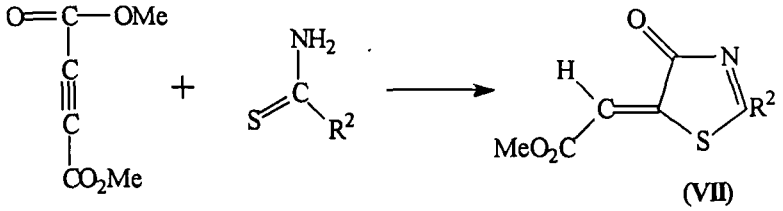


(VI)

L = OH, OEt

R^2 = alkyl, aryl, NR_2, OR, SR

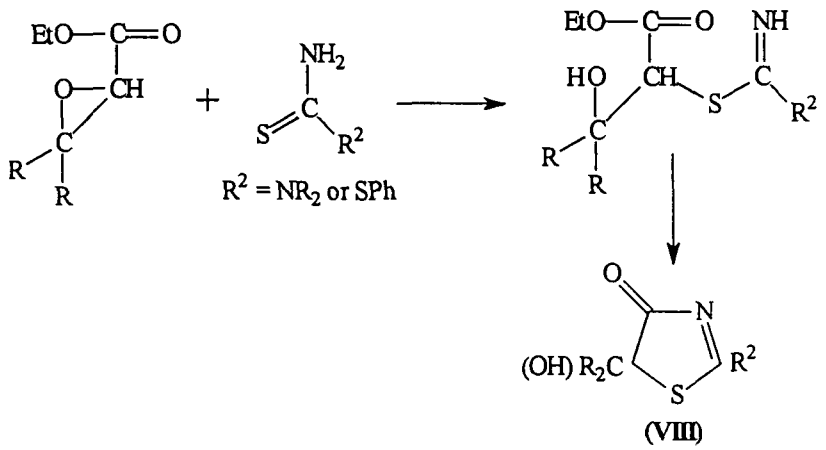
2-substituted 5-methoxy carbonylmethylene-Δ^2-thiazolin-4-ones[27](**VII**) were prepared from thioamides and thioureas with dimethylacetylene-dicarboxylates.



(VII)

R^2 = alkyl, NR_2

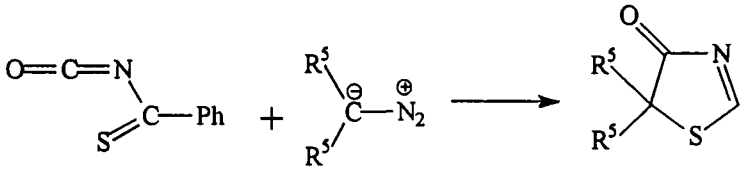
S. Gabrial *et al.*[28] have synthesized Δ^2-thiazolin-4-ones (**VIII**) from thiourea and phenyldithio carbamate (R^2=NR_2, SPh) with glycidic esters.



R^2 = NR_2 or SPh

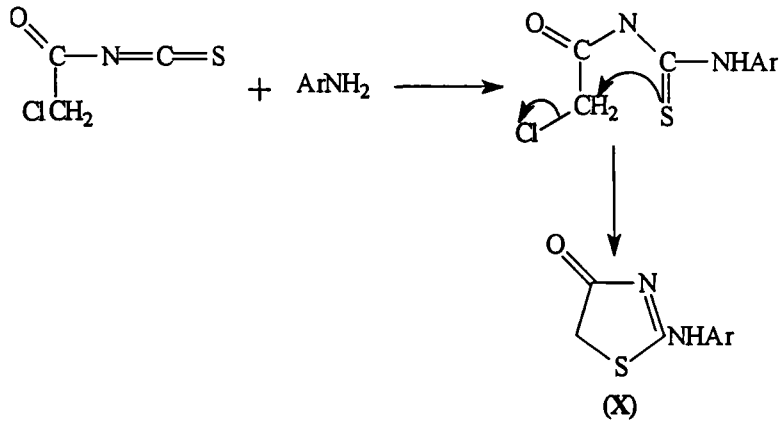
(VIII)

J. Goesdeler *et al.*[29] have prepared Δ^2-thiazolin-4-one derivatives (**IX**) from diazoalkanes by condensing with thiobenzoylisocynate.



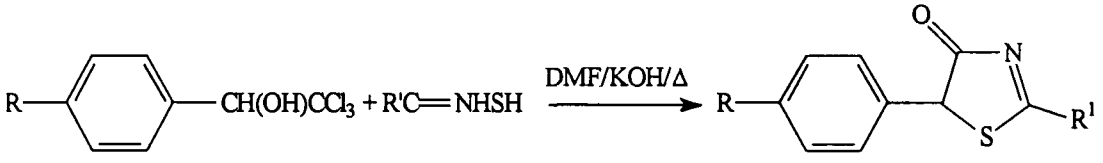
(IX)

2-arylamino-Δ^2-thiazolin-4-ones[30] (**X**) were prepared by the reaction of β-chloroethyl or acetyl isothiocyanates with aryl amines.



(X)

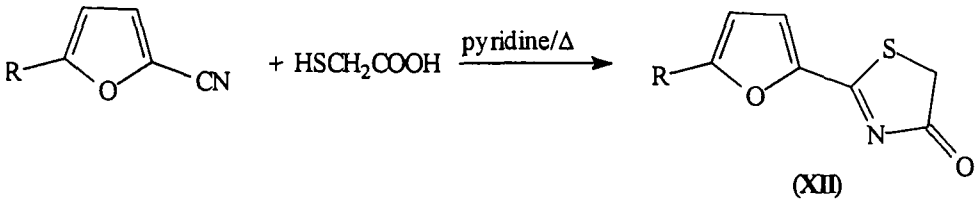
A.O. Gukasyan *et al.*[31] have synthesized 2,5-di-substituted thiazolin-4-ones (**XI**) from cyclocondensation of *p*-R-C_6H_4 CH(OH) CCl_3 with R^1C (:NH) SH in DMF in the presence of KOH.



(XI)

R = H, Me, Cl, Br, F
R^1 = Me, Ph

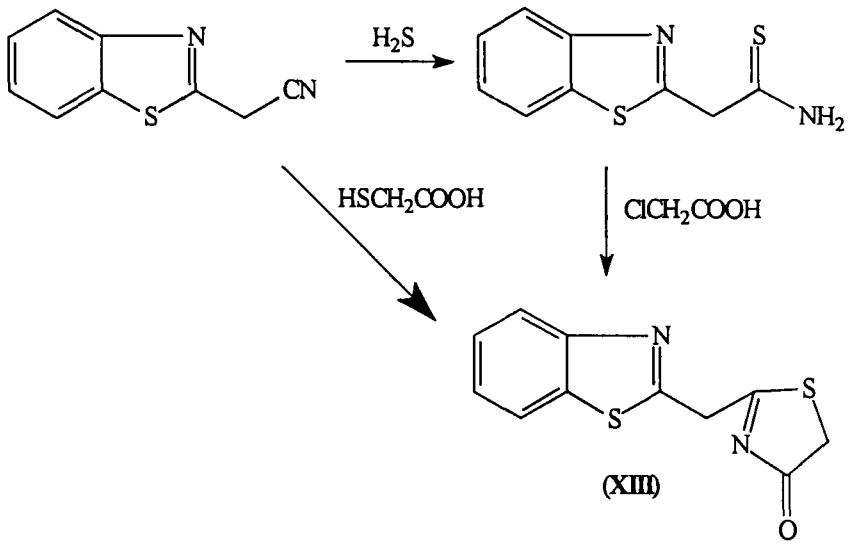
G.D. Krapivin *et al.*[32] have prepared 2-(5-R-2-furyl) thiazolin-4-ones **(XII)** from cyanofuran with thioglycollic acid in pyridine.



(XII)

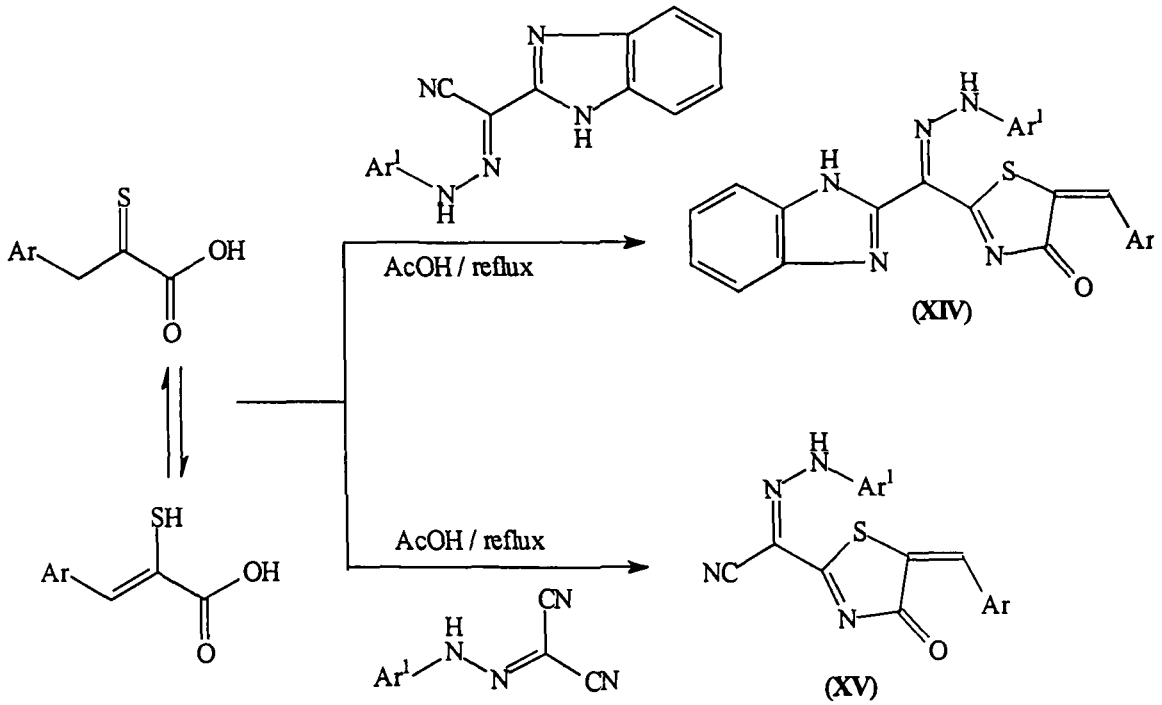
R = H, Me, NO_2, 2, 4, 6, Cl_3-C_6H_2

M.A.A. Elneairy *et al.*[33] have prepared 2-(1,3-benzothiazol-2-yl-methyl)-1,3-thiazol-4-(5H)-one **(XIII)** from 2-(1,3-benzothiazol-2-yl) acetonitrile with H_2S and chloroacetic acid. The same compound **(XIII)** was also obtained by using mercepto acetic acid.



(XIII)

Nadia H. Metwally[34] have synthesized 5-arylidene-2-(arylazocyano-methylene)-4,5-dihydrothiazol-4-ones **(XIV)** and 5-arylidene-2-(arylazo-methylenebenzimidazolyl)-4,5-dihydrothiazol-4-ones **(XI)** by refluxing 3-aryl-2-sulfanylacrylic acid with α-aryl hydrazononitriles and 2-arylhydrazono-2-cyanomethylbenzimidazoles in acetic acid.



	Ar
a	C_6H_5
b	4-$MeOC_6H_4$

	Ar	Ar^1
a	C_6H_5	C_6H_5
b	C_6H_5	4-MeC_6H_4
c	C_6H_5	4-$MeOC_6H_4$
d	C_6H_5	4-ClC_6H_4
e	4-$MeOC_6H_5$	C_6H_5
f	4-$MeOC_6H_5$	4-MeC_6H_4
g	4-$MeOC_6H_5$	4-$MeOC_6H_4$
h	4-$MeOC_6H_5$	4-ClC_6H_4

Discussion

DISCUSSION

SUMMARY

The work described in this chapter consists of the synthesis of following two novel compounds -

(i) 2-[3,5-bis(2-thienyl)-2-pyrazolin-1-yl]thiazolin-4-one ***SD$_{1B}$*** *(20) from 1,3-bis(2-thienyl)-2-propen-1-one (17) via 2-[3,5-bis(2-thienyl)-2-pyrazolin-1-yl]thiocarboxamide* ***SD$_{1A}$*** *(19) and*

(ii) 2-[3-(4-bromophenyl)-5-(4-methylphenyl)-2-pyrazolin-1-yl]thiazolin-4-one ***SD$_{7B}$*** *(24) from 4-bromophenyl-4-methylphenyl-2-propen-1-one (21) via 2-[3-(4-bromophenyl)-5-(4-methylphenyl)-2-pyrazolin-1-yl]thiocarboxamide* ***SD$_{7A}$*** *(23), both in (i) and (ii) using chloroacetic acid in the presence of sodium acetate*

Structures are established on the basis of IR, Mass, ^{1}H-NMR and ^{13}C-NMR spectral studies. The compounds (19) and (20) have been evaluated for anticancer activity and compounds (19) and (24) for antibacterial activity.

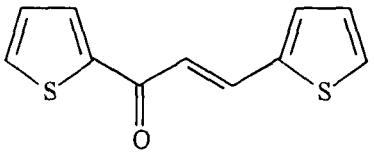
INTRODUCTION

In recent years, the synthesis of thiazolin-4-ones has received considerable attention because of their wide range of biological and pharmaceutical applications as antiulcer and cytoprotective[4], antimicrobial[5-6], antiallergic[7-8], antiinflammatory[9], antitubercular[10], antiproliferative[11], antibonedisorder[12], anti AIDS[13], cardiotonics[14-16], diabetes[17], fungicidal[18] and fibrinogen receptor[20]. Although a large number of thiosemicarbazones[24-26] of a variety of aldehydes and ketones (including indanone, flourenone, steroid, chromanone, chalcone and flavanone) have been prepared as intermediates for synthesis of various kinds of heterocyclic compounds[35-41] and for biological testing[24,26,39], some of these possess potential antitubercular[24,42] and antiviral[43] activities. The compounds containing thiophene ring have been

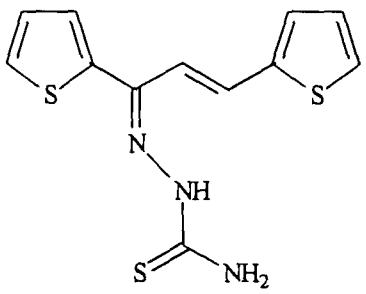
found to possess potent anthelmentic activity[48]. In recent past, reactions of thiosemicarbazones[24-26,33] of various aldehydes and ketones with α-chloroacetic acid and its functional derivatives in presence of sodium acetate have been investigated and found to give the corresponding hydrazono-thiazolin-4-ones. However, the analogous reactions of 3,5-disubstituted-2-pyrazolin-1-yl-thiocarboxamides with chloroacetic acid have not yet been described. Keeping in view of the importance of above findings and as part of our programme in search of biologically active compounds with sulphur and nitrogen containing heterocycles, we have undertaken this problem. In continuation of our previous work described in **CHAPTER - 2** on the reactions of thiosemicarbazide with different α,β-unsaturated dienones to form novel compounds, 3,5-diaryl substituted 2-pyrazolin-1-yl-thiocarboxamides, we have extended the above reactions employing the substrates, 2-thienylchalcone and 4,4'-bromomethyl chalcone in place of dienones and condensing the thiocarboxamide moiety of 2-pyrazolinyl thiocarboxamides with chloroacetic acid in presence of sodium acetate in order to incorporate a thiazolin-4-one ring in the molecule with a view to enhance biological and pharmaceutical properties. The substrates, *thienyl chalcone, 1,3-bis(2-thienyl)-2-propen-1-one* **(17)** and *bromomethyl chalcone, 1-(4-bromophenyl)-3-(4-methyl phenyl)-2-propen-1-one* **(21)** have been prepared following a reported procedure[47] by condensing 2-acetyl thiophene with thiophene-2-aldehyde (both prepared from reported method[47]) and 4-bromoacetophenone with tolualdehyde in presence of sodium hydroxide. The reactions of these chalcones possessing α,β-unsaturated function are then proceeded in two steps. The chalcones **(17)** and **(21)** are

first reacted with thiosemicarbazide in the presence of conc. HCl to yield *N^1-[1,3-bis(2-thienyl)-2-propen-1-ylidene]thiosemicarbazide* **(18)** (15%) and *2-[3,5-bis(2-thienyl)-2-pyrazolin-1-yl]thiocarboxamide* (65%) in the former while *N^1-[1-(4-bromophenyl)-3-(4-methylphenyl)-2-propen-1-ylidene]thiosemicarbazide* **(22)** (14%) and *2-[3-(4-bromophenyl)-5-(4-methylphenyl)-2-pyrazolin-1-yl]thiocarbaxamide* **(23)** (66%) in the later The pyrazolinyl thiocarboxamides **(19)** and **(23)** are then treated with chloroacetic acid in presence of sodium acetate to yield novel compounds, *2-[3,5-bis(2-thienyl)-2-pyrazolin-1-yl]thiazolin-4-one* **(20)** and *2-[3-(4-bromophenyl)-5-(4-methylphenyl)-2-pyrazolin-1-yl]thiazolin-4-one* **(24)** respectively

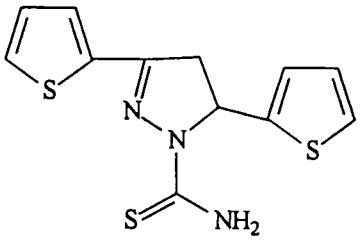
Structural assignments, stereochemistry and biological assay are discussed. Screening results of **(19)** and **(20)** are summarized for anticancer activity against 3-cell lines of three types of human cancers : lung, breast and CNS and compounds **(19)** and **(24)** for antibacterial activity. **(DETAILS IN CHAPTER-6).**



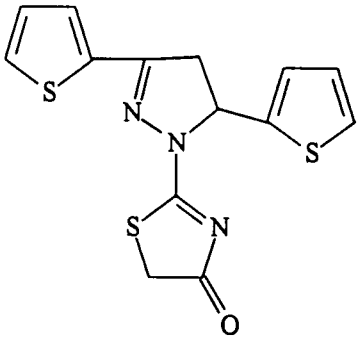
(17)



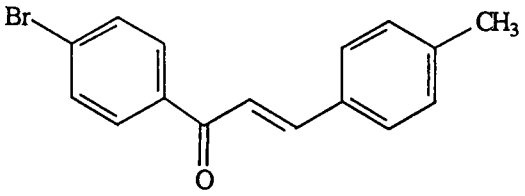
SD_1 (18)



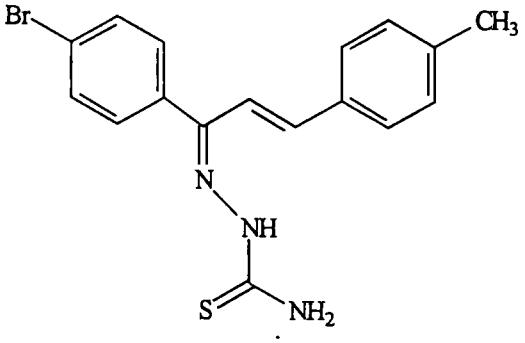
SD_{1A} (19)



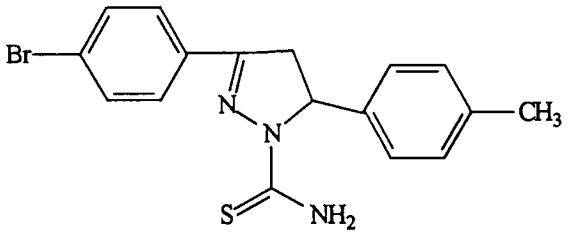
SD_{1B} (20)



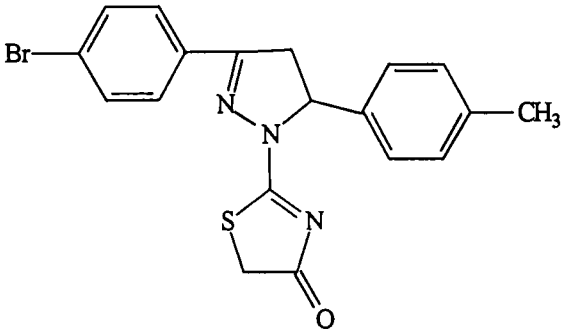
(21)



SD_7 (22)



SD_{7A} (23)



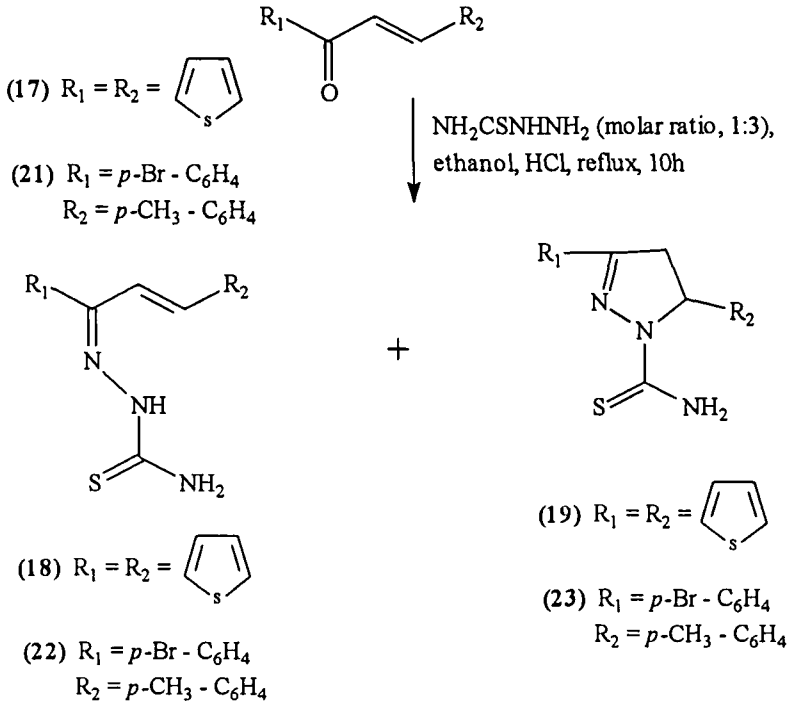
SD_{7B} (24)

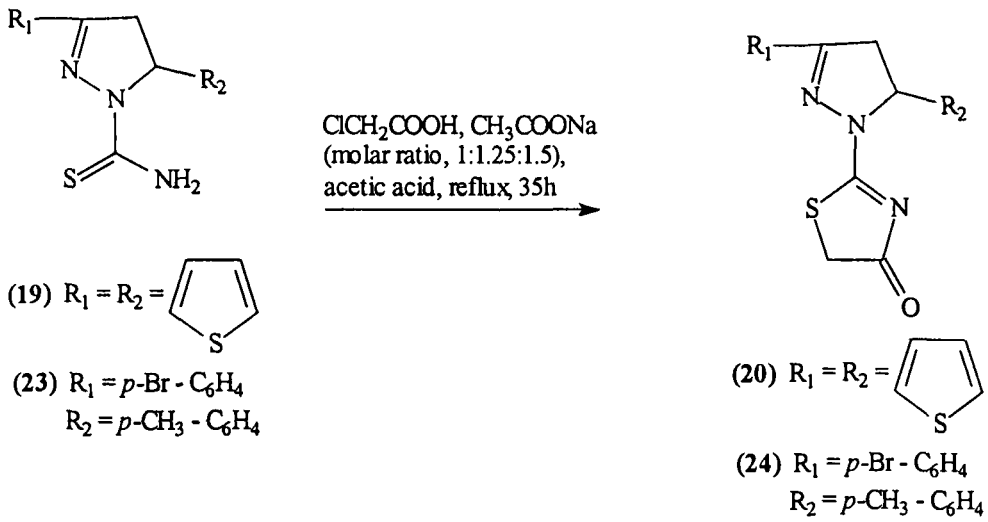
RESULTS AND DISCUSSION

The synthesis of target compounds (**20**) and (**24**) has been performed in two steps (**SCHEME-V**).

Step 1 : The 2-pyrazolinyl-thiocarboxamide (**19**) and (**23**) were first prepared as described in **CHAPTER-2** from chalcones (**17**) and (**21**) with thiosemicarbazide (molar ratio, 1:3) in absolute alcohol in presence of conc. HCl under reflux for 6-10 h in good yields (~65%, 66.%). The uncyclized thiosemicarbazones (**18**) and (**22**) formed as intermediate were also isolated in poor yields.

Step 2 : The compounds (**19**) and (**23**) were then condensed with chloroacetic acid and sodium acetate (molar ratio, 1:1.25:1.5) by refluxing the reaction mixture in freshly distilled acetic acid for 35 h. The respective products obtained after usual work up and purification by column chromatography over silica gel using benzene-ethyl acetate (8:2 v/v) as eluent followed by crystallization yielded (**20**) and (**24**) as brown crystalline needles in 56% and 55% yields.





(19) $R_1 = R_2 =$ thienyl

(23) $R_1 = p$-Br - C_6H_4
$R_2 = p$-CH_3 - C_6H_4

(20) $R_1 = R_2 =$ thienyl

(24) $R_1 = p$-Br - C_6H_4
$R_2 = p$-CH_3 - C_6H_4

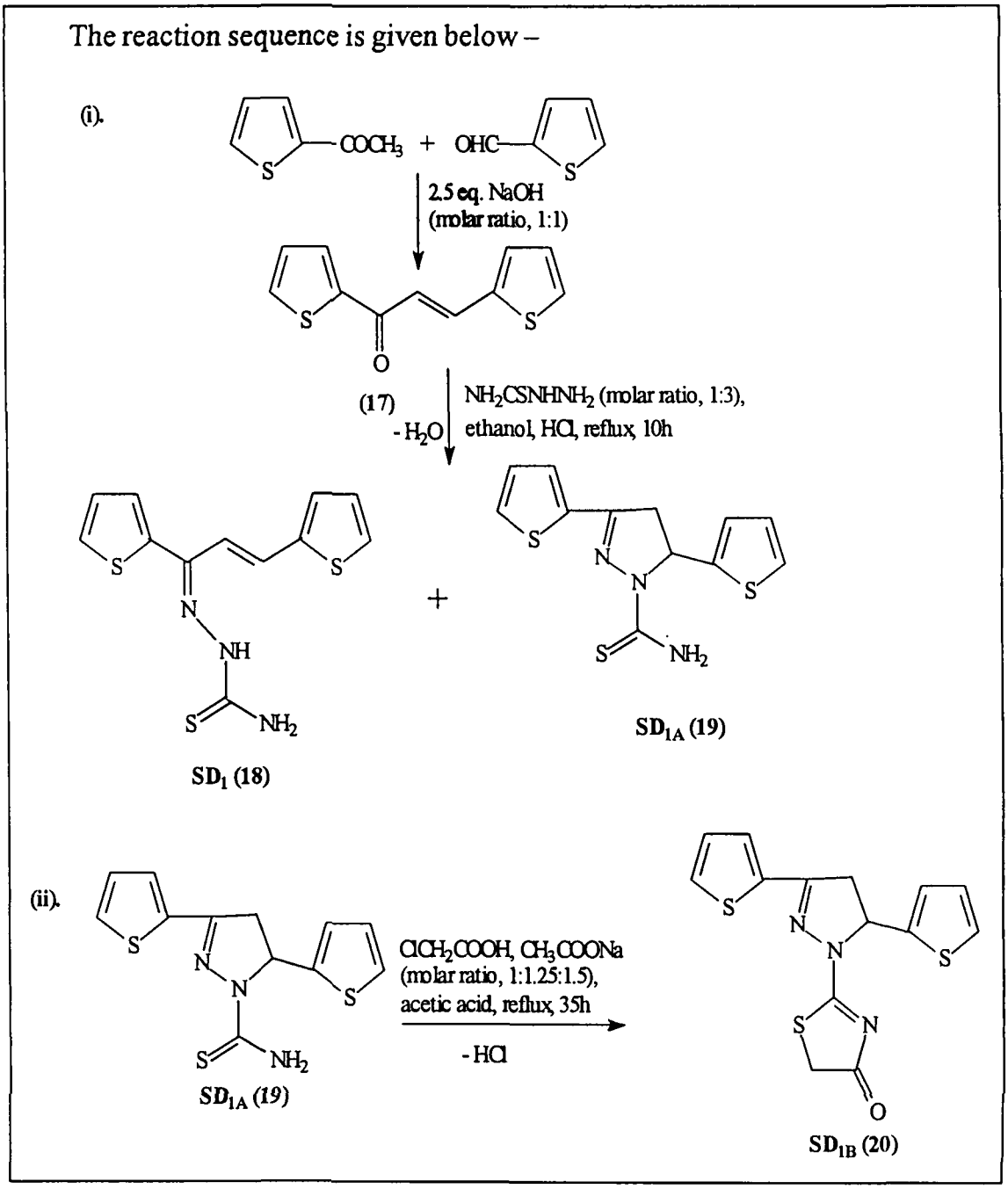
SCHEME - V

Synthesis of 2-[3,5-bis(2-thienyl)-2-pyrazolin-1-yl]thiazolin-4-one SD_{1B} (20) from 1,3-bis(2-thienyl)-2-propen-1-one (17) via 2-[3,5-bis(2-thienyl)-2-pyrazolin-1-yl]thiocarboxamide SD_{1A} (19) using chloroacetic acid in the presence of sodium acetate

The pyrazolinyl thiocarboxamide SD_{1A} (19) was first prepared by refluxing a solution of thiosemicarbazide and thienyl chalcone, 1,3-bis(2-thienyl)-2-propen-1-one (17) (molar ratio, 1:3) in absolute alcohol in presence of conc. HCl, for 10 h. After completion of the reaction, the reaction mixture on TLC examination (silica gel 'G' benzene-ethyl acetate, 8:2 v/v) showed the presence of two spots, labelled as SD_1 and SD_{1A}. On usual work up and purification by column chromatography (silica gel, benzene-ethyl acetate, 8:2 v/v) followed by crystallization from benzene-acetone, it yielded SD_1 as orange crystalline needles and SD_{1A} as brown crystalline needles in 15% and 65% yield respectively. The compound SD_{1A}(19) was then condensed with chloroacetic acid and sodium acetate (molar ratio, 1:1.25:1.5). The cyclocondensation was carried out by refluxing the reaction mixture in freshly distilled acetic acid for 35 h. TLC examination (silica gel

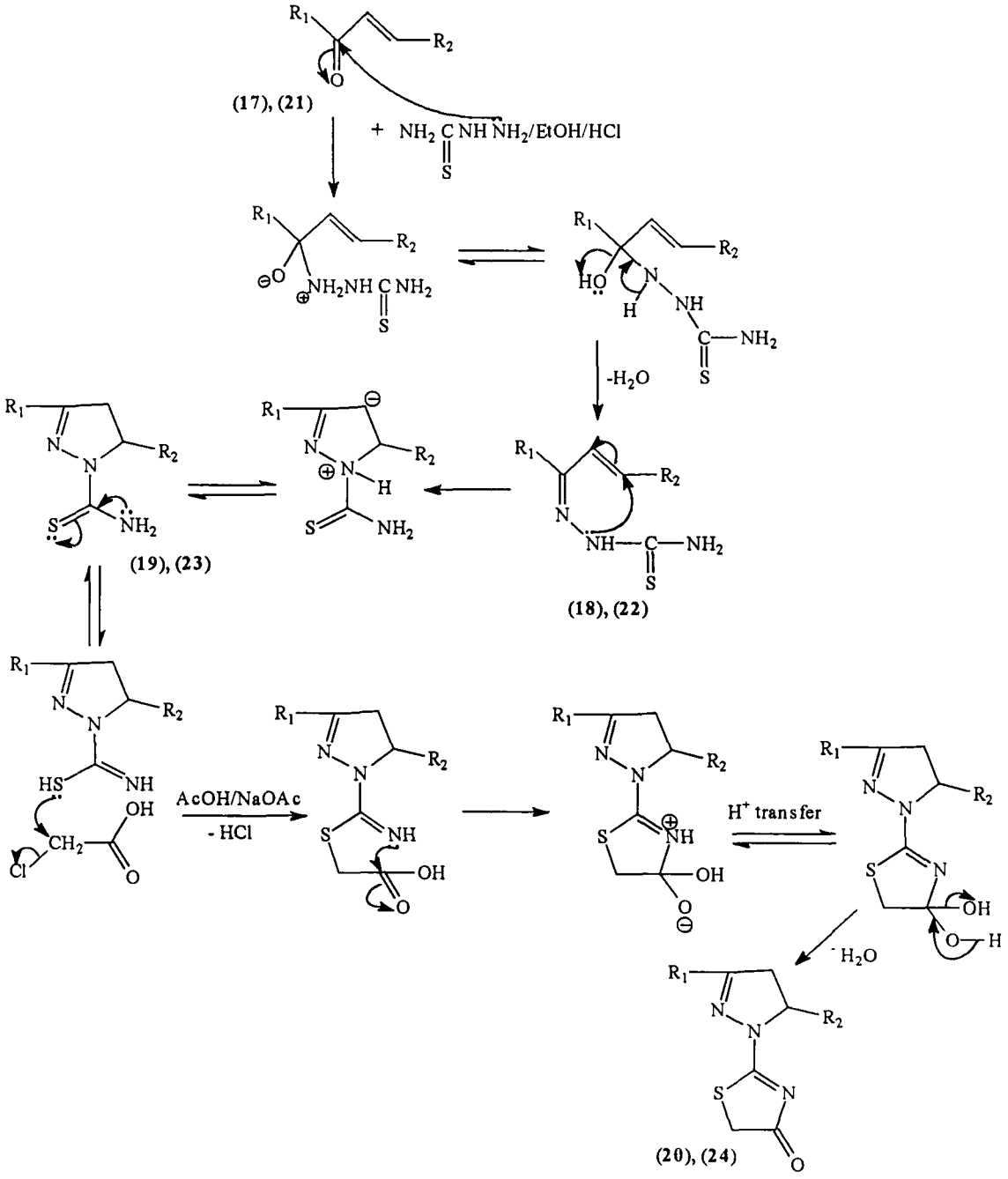
'G' benzene-ethyl acetate, 8:2 v/v) of the reaction mixture showed the presence of only one spot, labelled as SD_{1B}. After usual work up and purification of the products by column chromatography over silica gel using benzene-ethyl acetate (8:2 v/v) as eluent followed by crystallization (benzene-ethyl acetate, 9:1 v/v) yielded SD_{1B} **(20)** as brown crystalline needles in 56% yield.

The reaction sequence is given below –



Mechanism of the above reactions :

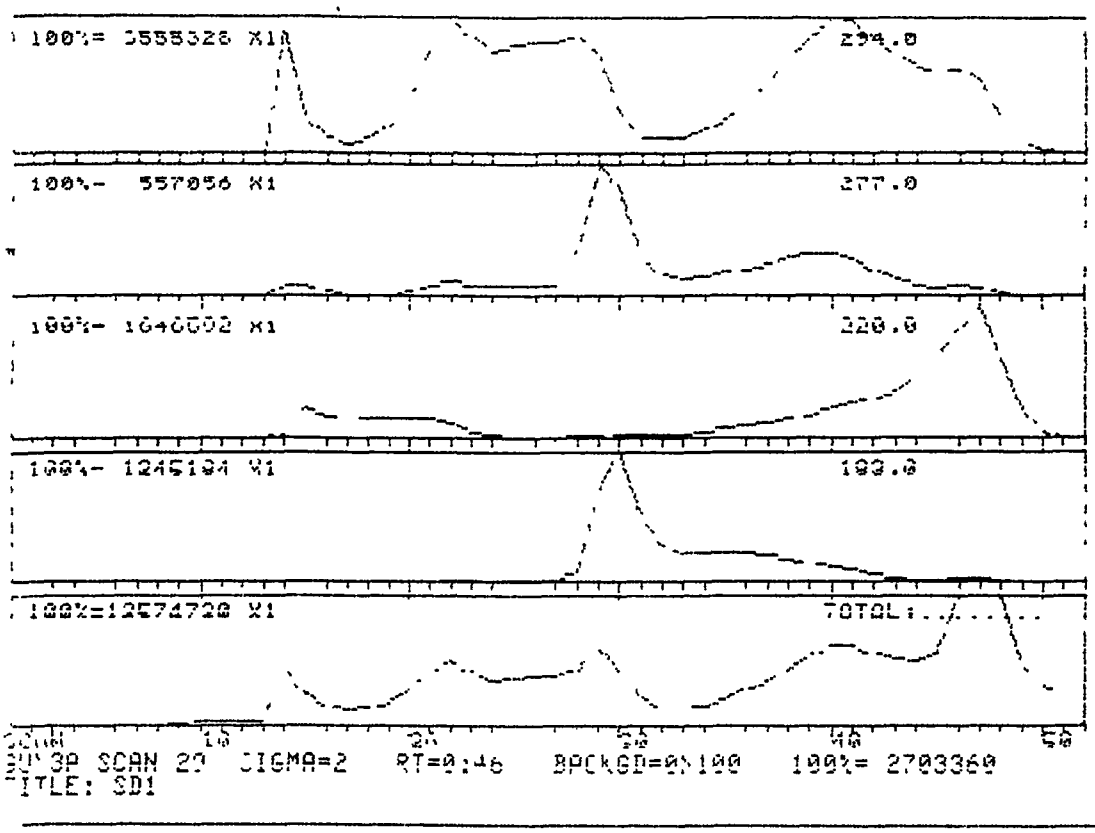
A plausible mechanism for the above reactions may be offered (**SCHEME-VI**). The 4-thiazolinone ring in SD_{1B} (**20**) and SD_{7B} (**24**) is believed to be formed by the cyclocondensation of the chloroacetic acid with thiocarboxamide moiety of 2-pyrazolines SD_{1A} (**19**) and SD_{7A} (**23**).

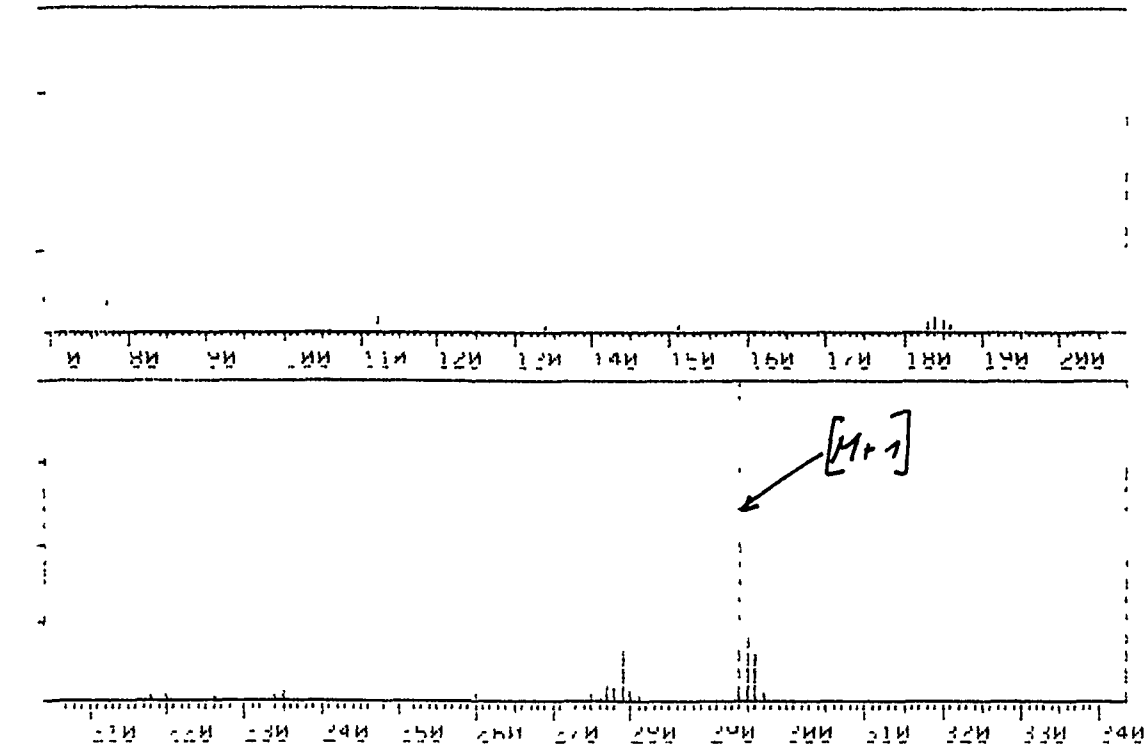


SCHEME - VI

Structure Elucidation of SD_1 (18)

It is an orange crystalline solid,m.p. 130 °C and appears brown on exposure to iodine vapours (TLC). The structure of **SD_1** has been established by FT-IR, DCI-MS, ^{1}H-NMR and ^{13}C-NMR spectra. IR spectrum (KBr pellets) of **SD_1** showed characteristic signals at 3420, 3240 (NH), 2915 (CH), 1590 (C=N), 1495 (phenyl), 1180 (C=S), 1070 (C-N), 950, 816, 715 cm^{-1}. The DCI-MS (NH_3 as reagent gas) spectrum **(FIG. 37)** of **SD_1 (18)** showed $[M+H]^+$ peak at m/z 294 as the base peak, confirming its molecular weight 293. This is equal to the sum of the molecular weights of *1,3-bis(2-thienyl)-2-propen-1-one* **(17)** (220) and thiosemicarbazide (91) minus one molecule of water (18) indicating that condensation has occurred between the carbonyl group of the chalcone and amino group of semicarbazide forming thiosemicarbazone. A peak appeared at m/z 260 $[(M+H)-H_2S]^+$ was due to the loss of H_2S and another peak at m/z 277 $[(M+H)-NH_3]^+$ observed by the loss of ammonia from parent ion. The other important fragment ion peaks were observed at m/z 233, 183, 112 and 77. These supported the thiosemicarbazone structure **(CHART-12)**. The ^{1}H-NMR **(FIG. 38)** and ^{13}C-NMR **(FIG. 39)** spectra of **SD_1** dissolved in acetone-d_6 showed signals as assinged **(TABLE-13)**. The assignments of all ^{1}H-NMR and ^{13}C-NMR signals to specific H- and C-atoms have been performed on the basis of typical chemical shift values, multiplicity, relative integrations and also by comparison of the spectral data with that of *1,3-bis(2-thienyl)-2-propen-1-one* (Experimental). The ^{1}H-NMR of **SD_1** showed two doublets at δ7.21 (J=16.02 Hz) and δ7.44 (J=16.02 Hz) which were attributed to C-2 and C-3 protons. The proton at C-3 appeared at lower field (δ7.44) as compared to proton at C-2 (δ7.21) as a consequence of deshielding effect of 2-thienyl group attached to it. The coupling constant (J=16.02 Hz) suggested that the





77 00	3 7	185 00	3 1	277 00	20 6	294 00	100 0
112 00	3 6	233 00	3 6	278 00	4 3	295 00	21 1
133 00	32 4	235 00	3 9	279 00	18 0	296 00	15 4
184 00	4 3	260 00	3 1	280 00	3 1		

FIG. 37

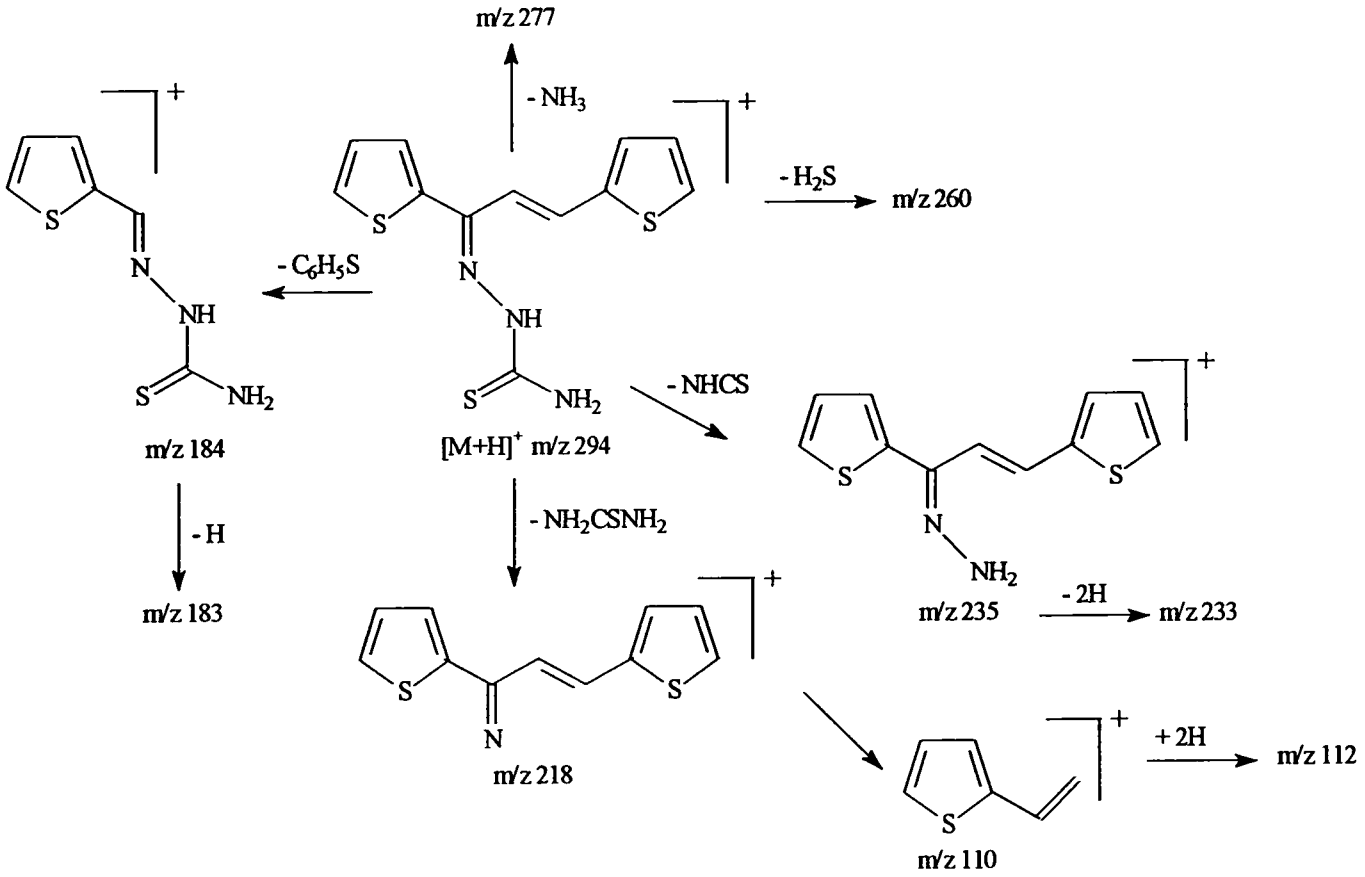

m/z 277
- NH3
- H2S
m/z 260
- C6H5S
- NHCS
m/z 184
[M+H]+ m/z 294
- H
m/z 183
- NH2CSNH2
m/z 235
- 2H
m/z 233
m/z 218
+ 2H
m/z 112
m/z 110

CHART - 12

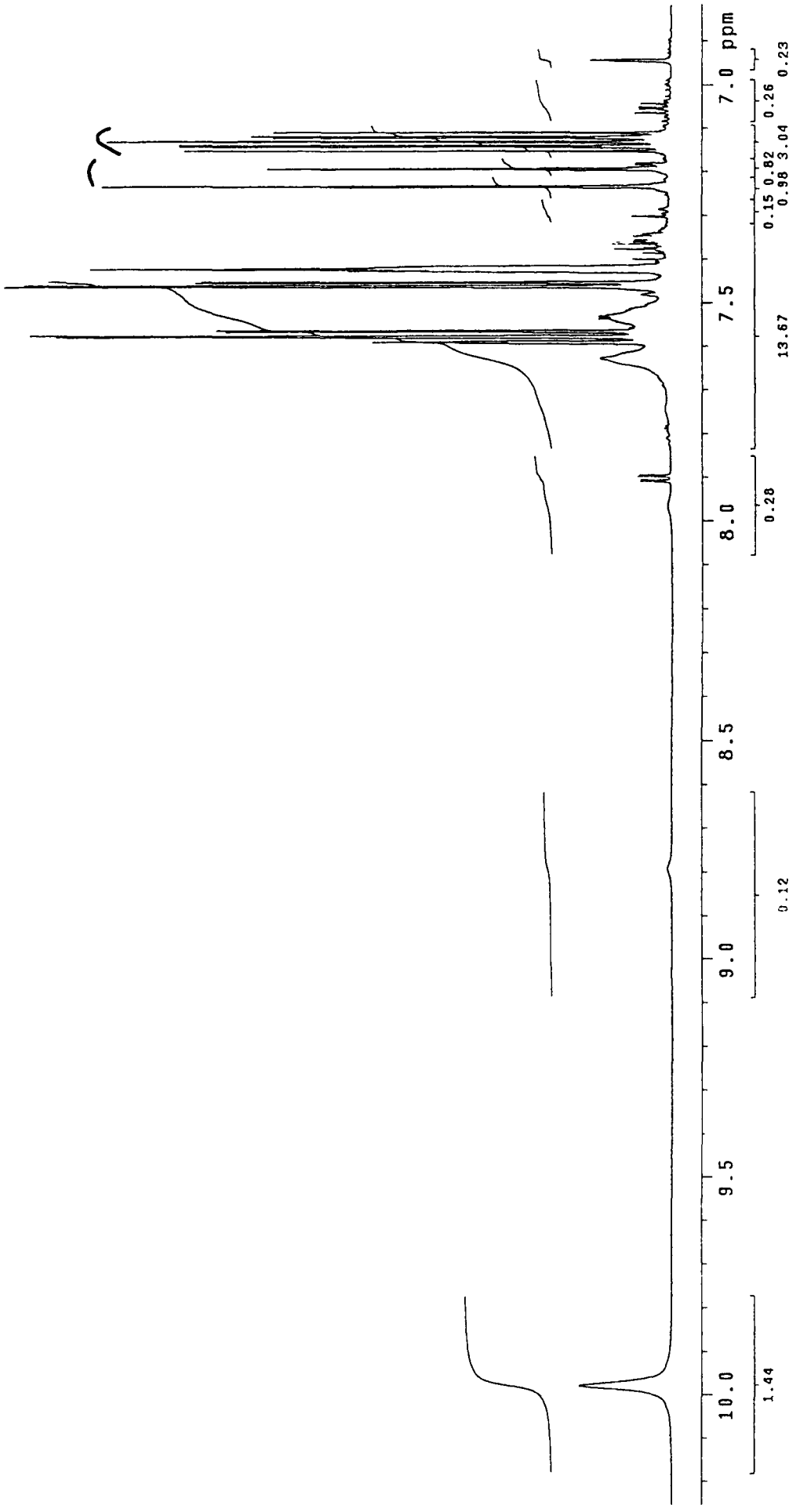
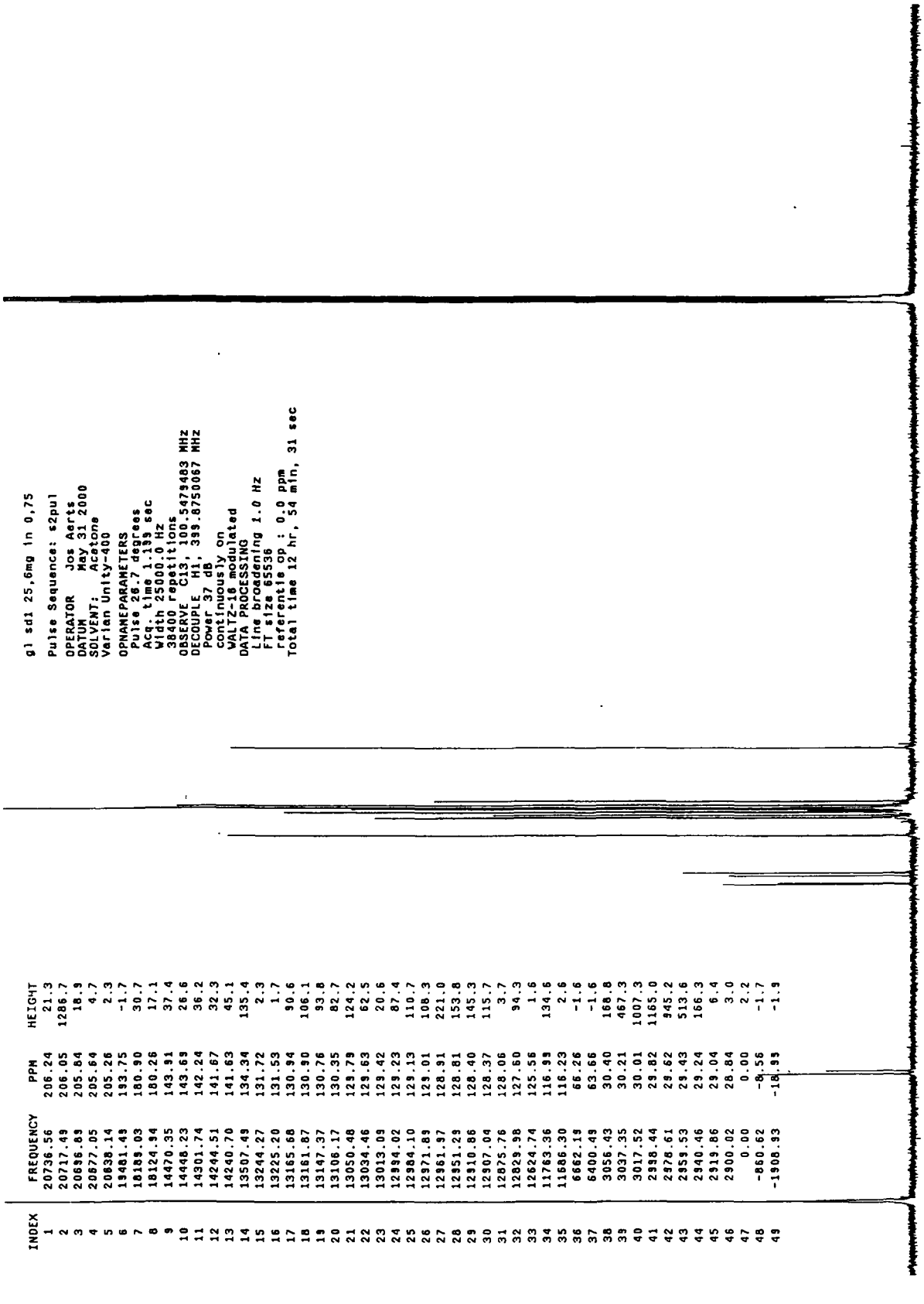


FIG. 38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Pulse Sequence: s2pul
OPERATOR Jos Aerts
DATUM May 31 2000
SOLVENT: Acetone
Varian Unity-400
OPNAMEPARAMETERS
Pulse 26.7 degrees
Acq. time 1.139 sec
Width 25000.0 Hz
38400 repetitions
OBSERVE C13, 100.5479483 MHz
DECOUPLE H1, 399.8750067 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
referentie op : 0.0 ppm
Total time 12 hr, 54 min, 31 sec
INDEX FREQUENCY PPM HEIGHT
1 20736.56 206.24 21.3
2 20717.49 206.05 1286.7
3 20686.83 205.84 18.9
4 20677.05 205.64 4.7
5 20638.14 205.26 2.3
6 19481.49 193.75 -1.7
7 18189.03 180.90 30.7
8 18124.94 180.26 17.1
9 14470.35 143.91 37.4
10 14448.23 143.69 26.6
11 14301.74 142.24 36.2
12 14244.51 141.67 32.3
13 14240.70 141.63 45.1
14 13507.49 134.34 135.4
15 13244.27 131.72 2.3
16 13225.20 131.53 1.7
17 13165.68 130.94 90.6
18 13161.87 130.90 106.1
19 13147.37 130.76 93.8
20 13106.17 130.35 82.7
21 13050.48 129.79 124.2
22 13034.46 129.63 62.5
23 13013.09 129.42 20.6
24 12994.02 129.23 87.4
25 12984.10 129.13 110.7
26 12971.89 129.01 108.3
27 12961.97 128.91 221.0
28 12951.29 128.81 153.8
29 12910.86 128.40 145.3
30 12907.04 128.37 115.7
31 12875.76 128.06 3.7
32 12829.98 127.60 94.3
33 12624.74 125.56 1.6
34 11763.36 116.99 134.6
35 11686.30 116.23 2.6
36 6662.19 66.26 -1.6
37 6400.49 63.66 -1.6
38 3056.43 30.40 168.8
39 3037.35 30.21 467.3
40 3017.52 30.01 1007.3
41 2998.44 29.82 1165.0
42 2978.61 29.62 945.2
43 2959.53 29.43 513.6
44 2940.46 29.24 166.3
45 2919.86 29.04 6.4
46 2900.02 28.84 3.0
47 0.00 0.00 2.2
48 -860.62 -8.56 -1.7
49 -1908.93 -18.98 -1.9
200 180 160 140 120 100 80 60 40 20 0 ppm

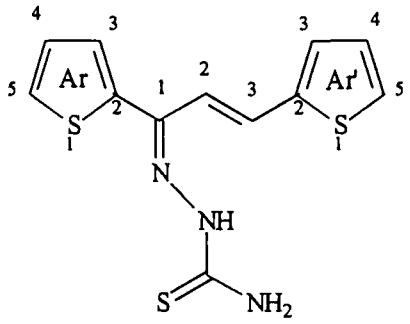
FIG. 39

TABLE -13 : ^{1}H-NMR and ^{13}C-NMR spectral data of SD_1 (18)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)	C-nr	δ (ppm)
2	7.21	1H	d	$J_{2,3}$=16.02	2	116.99
3	7.44	1H	d	$J_{2,3}$ = 16.02	3	134.34
NH_2	7.53, 7.63	2H	s	–	1	143.69
NH	9.98	1H	s	–	C=S	180.90
Ar + Ar'	7.11-7.60	6H	br m	–	Ar + Ar'	127.60-143.91

ethylenic protons were trans to each other. A broad singlet at δ9.98 was observed for NH proton and two singlets at δ7.53 and δ7.63 were also appeared for NH_2 protons. The aromatic protons signals as broad multiplet at δ7.11 - 7.60 for two 2-thienyl rings were accounted for six protons. The ^{13}C-NMR spectrum also confirmed the formation of thiosemicarbazone as C-1 signal of carbonyl carbon has shifted to higher field from δ181.80 to 143.69 due to disappearance of C=O group and formation of C=N group. Two signals at δ116.99 and δ134.34 were assigned to C-2 and C-3 carbons. The signal at δ180.90 was attributed to C=S carbon. The aromatic carbons signals were assigned as shown in **TABLE-13**.

On the basis of these facts, $\mathbf{SD_1}$ was characterized as *N^1-[1,3-bis(2-thienyl)-2-propen-1-ylidene]thiosemicarbazide* ***(18)***.



SD_1 (18)

Structure Elucidation of SD_{1A} (19)

It is a brown needle shaped crystalline solid, m.p. 138 °C and appears brown on exposure to iodine vapours (TLC). The structure of $\mathbf{SD_{1A}}$ has been established by FT-IR, DCI-MS, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum (KBr) displayed characteristic absorption bands at 3436 (NH), 2945 (CH), 1576 (C=N), 1463 (phenyl), 1339, 1171 (C=S), 1079 (C-N), 906, 818, 721, 609 cm^{-1}. The DCI-MS spectrum **(FIG. 40)** of $\mathbf{SD_{1A}}$ showed a

$[M+1]^+$ peak at m/z 294 as the base peak, confirming its molecular weight 293 [$C_{12}H_{11}N_3S_3$]. This is equal to the sum of the molecular weights of **(17)** (220) and thiosemicarbazide (91) minus one molecule of water (18) which indicated that the condensation has occurred between the thienylchalcone and thiosemicarbazide. The peak at m/z 260 $[(M+1) - H_2S]^+$ was arised due to the loss of H_2S from the parent ion and an another peak at m/z 234 $[(M+1) - CSNH_2]^+$ appeared by the cleavage of N-C bond. The peak observed at m/z 218 $[(M+1) - NH_2CSNH_2]^+$ was due to the cleavage of 1-2 and 1-5 bonds, showing the location of the ring. The peak at m/z 183 $[(M+1) - C_5H_5NS]^+$ and m/z 109 $[(M+1) - C_7H_9N_2S_2]^+$ arised due to fragmenting of the ring at 1-2 and 3-4 bonds which further confirmed the formation of ring. The other important fragement ions were observed at m/z 171, 169, 151, 109, all these supported the formation of pyrazoline ring **(CHART-13)**. The ^{1}H-NMR **(FIG. 41)** and ^{13}C-NMR **(FIG. 42)** dissolved in acetone-d_6 showed signals as assigned **(TABLE-14)**. The assignments of all ^{1}H- and ^{13}C-NMR signals to individual H- and C-atoms have been performed on the basis of typical chemical shift values, multiplicity and relative integrations and also by comparison with the spectral data of **SD_1 (18) (TABLE-13).** In ^{1}H-NMR spectrum, the disappearance of the signals corresponding to olefinic protons at δ7.21 (H-2) and δ7.44 (H-3) in **SD_1 (18)** and in place the appearance of new signals as two doublets at δ3.42 (J=17.55 Hz, J=2.75 Hz) and δ4.00 (J=17.55 Hz, J=10.84 Hz) were attributed to H-4eq and H-4ax respectively. A double doublet at δ6.37 (J=2.75 Hz, J=10.84 Hz) was assigned to H-5ax proton. Thus, the coupling constants showed that the two diastereotopic hydrogens at C-4 are anti and synperiplanar with C-5 hydrogen. The aromatic protons signals were accounted for six protons of two aromatic rings as shown in **TABLE-14**. The structure was further confirmed by ^{13}C-NMR spectrum

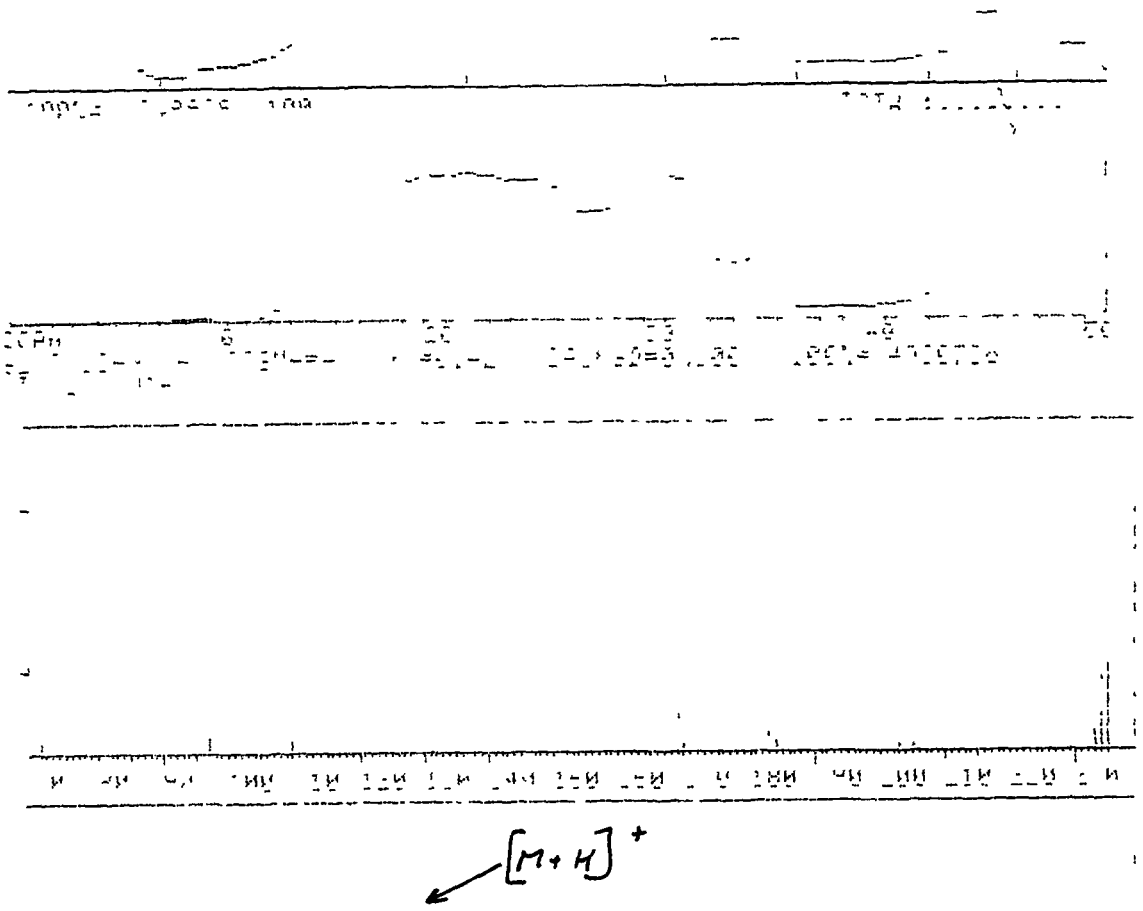
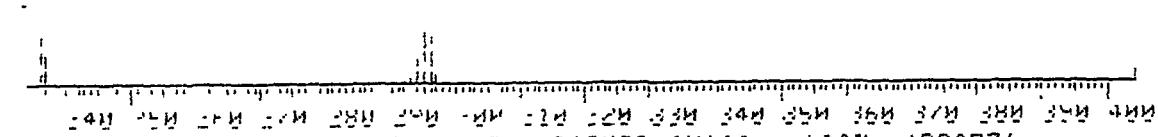


FIG. 40



SL13 SCAN 24 SIGMA=4 RT=0.42 BACKGD=0X100 100%= 4980736
TITLE SD1A

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139.00	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	296.00	15.[illegible]
151.00	[illegible]	[illegible]	[illegible]	260.00	[illegible]		
169.00	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		
171.00	4.1	235.00	9[illegible].1	[illegible]	100.0		

IN

START = 1 END = 31
TOTAL
235.0 [illegible]4691664
254.0 [illegible]1745244

#PA

ACQUISITION PARAMETER TABLE

MASS RANGE [illegible]-550
INTEGRATION TIMES
TYPE OF RUN MLM IFSL

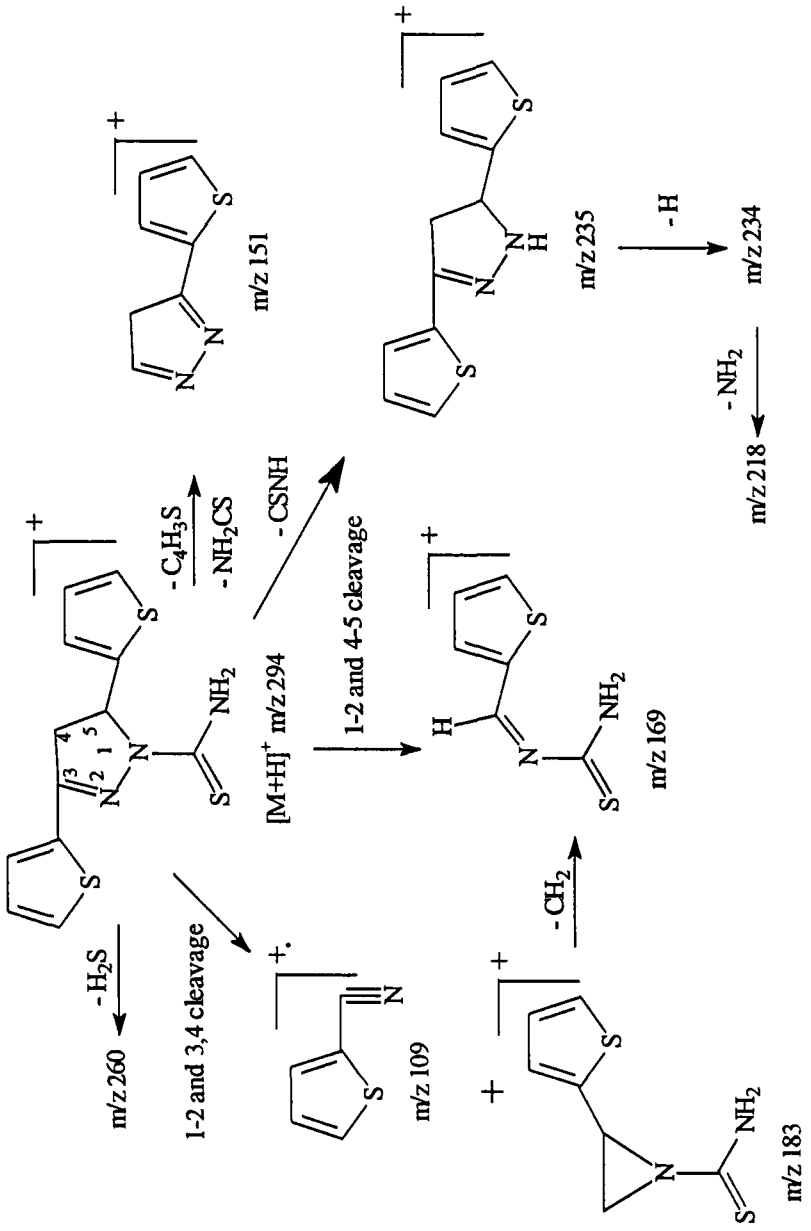

-H2S
m/z 260
1-2 and 3,4 cleavage
m/z 109
-C4H3S
-NH2CS
m/z 151
[M+H]+ m/z 294
-CSNH
1-2 and 4-5 cleavage
m/z 169
-CH2
m/z 183
m/z 235
-H
m/z 234
-NH2
m/z 218

CHART - 13

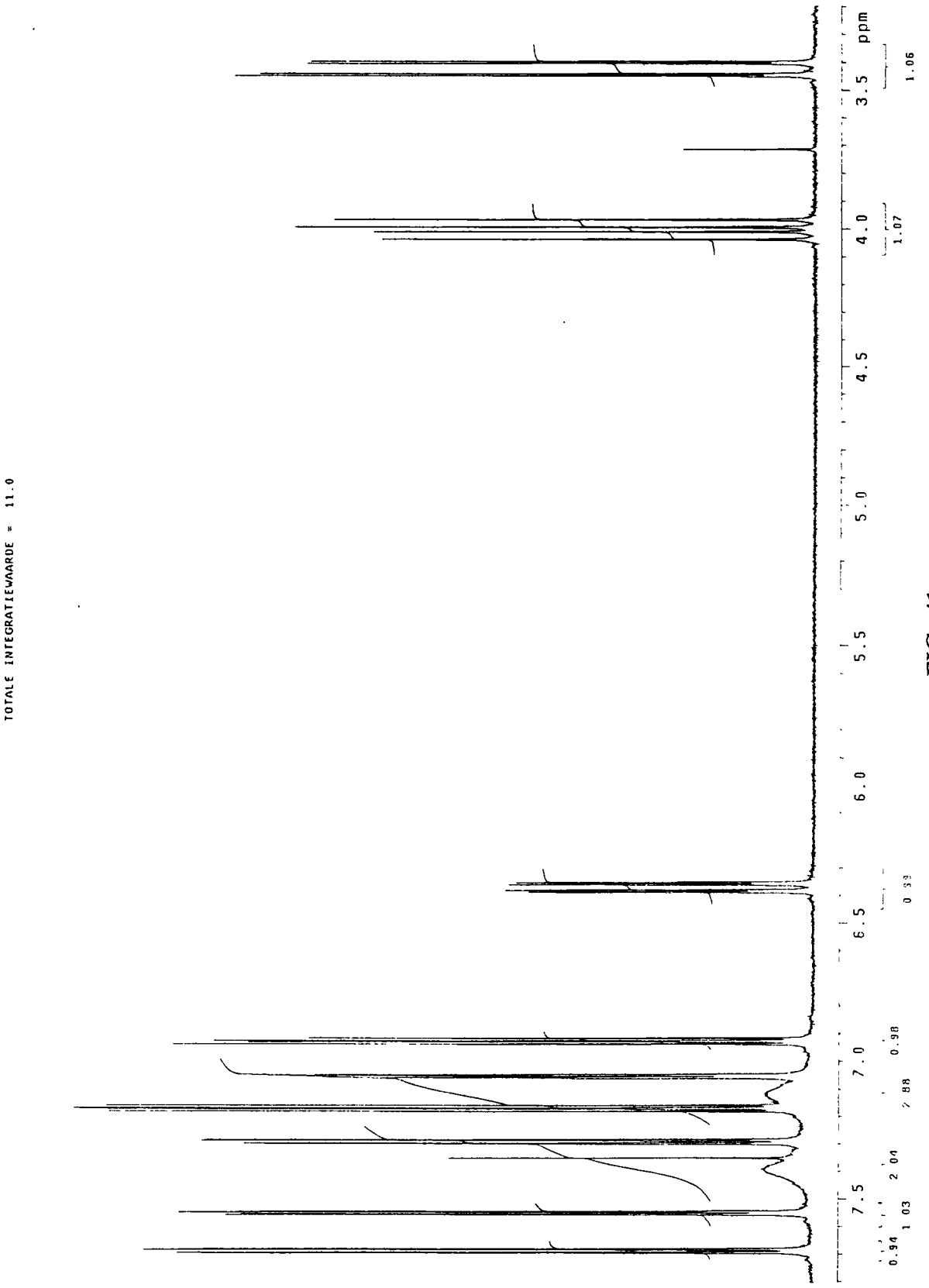

TOTALE INTEGRATIEWAARDE = 11.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
0.94
1.03
2.04
2.88
0.98
0.39
1.07
1.06

FIG. 41

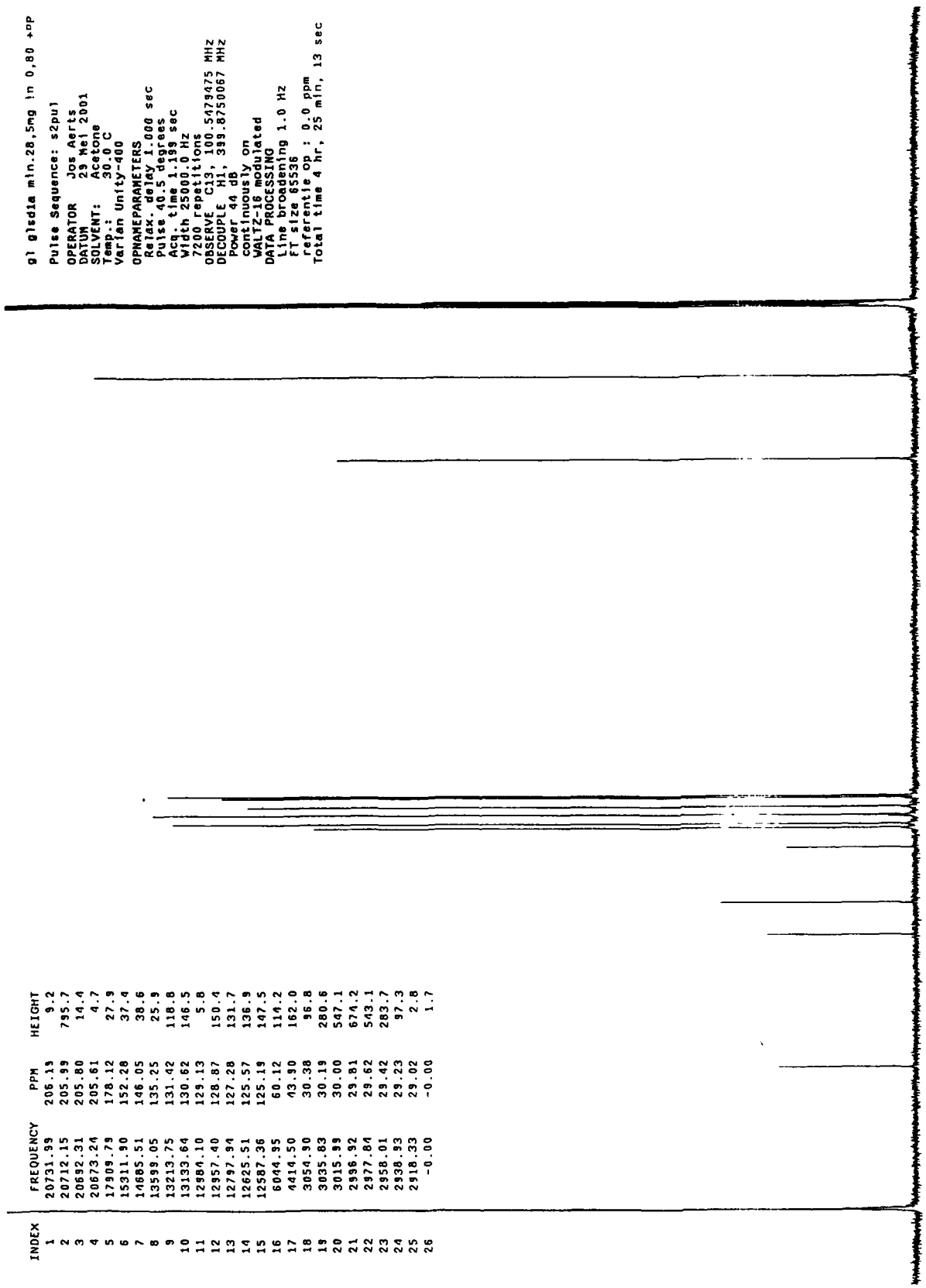

gl glsdia min.28,5mg in 0,80 +DP
Pulse Sequence: s2pul
OPERATOR Jos Aerts
DATUM 29 Mei 2001
SOLVENT: Acetone
Temp.: 30.0 C
Varian Unity-400
OPNAMEPARAMETERS
Relax. delay 1.000 sec
Pulse 40.5 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
7200 repetitions
OBSERVE C13, 100.5479475 MHz
DECOUPLE H1, 399.8750067 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
referentie op : 0.0 ppm
Total time 4 hr, 25 min, 13 sec
INDEX FREQUENCY PPM HEIGHT
1 20731.99 206.13 9.2
2 20712.15 205.99 795.7
3 20692.31 205.80 14.4
4 20673.24 205.61 4.7
5 17909.79 178.12 27.9
6 15311.90 152.28 37.4
7 14685.51 146.05 38.6
8 13599.05 135.25 25.9
9 13213.75 131.42 118.8
10 13133.64 130.62 146.5
11 12984.10 129.13 5.8
12 12957.40 128.87 150.4
13 12797.94 127.28 131.7
14 12625.51 125.57 136.9
15 12587.36 125.19 147.5
16 6044.95 60.12 114.2
17 4414.50 43.90 162.0
18 3054.90 30.38 96.8
19 3035.83 30.19 280.6
20 3015.99 30.00 547.1
21 2996.92 29.81 674.2
22 2977.84 29.62 543.1
23 2958.01 29.42 283.7
24 2938.93 29.23 97.3
25 2918.33 29.02 2.8
26 -0.00 -0.00 1.7
200 180 160 140 120 100 80 60 40 20 0 ppm

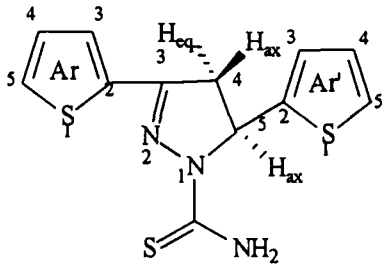
FIG. 42

TABLE -14 : ^{1}H-NMR and ^{13}C-NMR spectral data of SD_{1A} (19)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)	C-nr	δ (ppm)
4eq	3.42	1H	dd	$J_{4eq,4ax}$=17.55, $J_{4eq,5ax}$=2.75	3	135.25
4ax	4.00	1H	dd	$J_{4eq,4ax}$=17.55, $J_{4ax,5ax}$=10.84	4	43.90
5ax	6.37	1H	dd	$J_{4eq,5ax}$=2.75, $J_{4ax,5ax}$=10.84	5	60.12
NH_2	7.12, 7.40	2H	s	–	C=S	178.12
Ar-3	7.05	1H	ddd	$J_{Ar\text{-}3,4}$=3.66, $J_{Ar\text{-}3,5}$=1.22	Ar-2	152.28
				$J_{Ar\text{-}3,5ax}$=0.77	Ar-3	131.42
Ar-4	6.94	1H	dd	$J_{Ar\text{-}3,4}$=3.66, $J_{Ar\text{-}4,5}$=5.04	Ar-4	128.87
Ar-5	7.30	1H	dd	$J_{Ar\text{-}4,5}$=5.04, $J_{Ar\text{-}3,5}$=1.22	Ar-5	125.57
Ar'-3	7.55	1H	dd	$J_{Ar'\text{-}3,4}$=3.66, $J_{Ar'\text{-}3,5}$=1.07	Ar'-2	146.05
Ar'-4	7.17	1H	dd	$J_{Ar'\text{-}3,4}$=3.66, $J_{Ar'\text{-}4,5}$=5.04	Ar'-3	130.62
Ar'-5	7.69	1H	dd	$J_{Ar'\text{-}4,5}$=5.04, $J_{Ar'\text{-}3,5}$=1.07	Ar'-4	127.28
					Ar'-5	125.19

which also showed the disappearance of the signals corresponding to the ethylenic carbons at δ116.99 (C-2) and δ134.34 (C-3) in **SD_1 (18)** and the appearance of new signals corresponding to methylene carbon at δ43.90 (C-4) and methine carbon at δ60.12 (C-5). A signal at δ178.12 was assigned to C=S carbon and the signals for aromatic carbons appeared are shown in **TABLE-14**.

Based on the above spectral evidence, **SD_{1A}** was characterized as *2-[3,5-bis(2-thienyl)-2-pyrazoline-1-yl]thiocarboxamide* ***(19)***.



SD_{1A} (19)

Structure Elucidation of SD_{1B} (20)

It is a dark brown needle shaped crystalline solid, m.p. 280 °C and appears brown on exposure to iodine vapours on TLC. The constitution of **SD_{1B} (20)** has been established by FT-IR, DCI-MS, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum (KBr) of **SD_{1B}** displayed characteristic absorption bands at 2818 (CH), 1680 (C=O), 1593 (C=N), 1550 (phenyl), 1470 (S-CH_2), 1385, 1351, 1291, 1224, 1101, 829, 714 cm^{-1}. The DCI-MS (NH_3 as a reagent gas) spectrum of **SD_{1B} (FIG. 43)** showed $[M+H]^+$ peak at m/z 334 as the base peak, confirming its molecular weight 333. This is equal to the sum of the molecular weights of **SD_{1A}** (293) and chloroacetic acid (94) minus one molecule of water (18) as well as one molecule of HCl (36) which indicated that cyclocondensation has occurred between thiocarboxamide moiety of

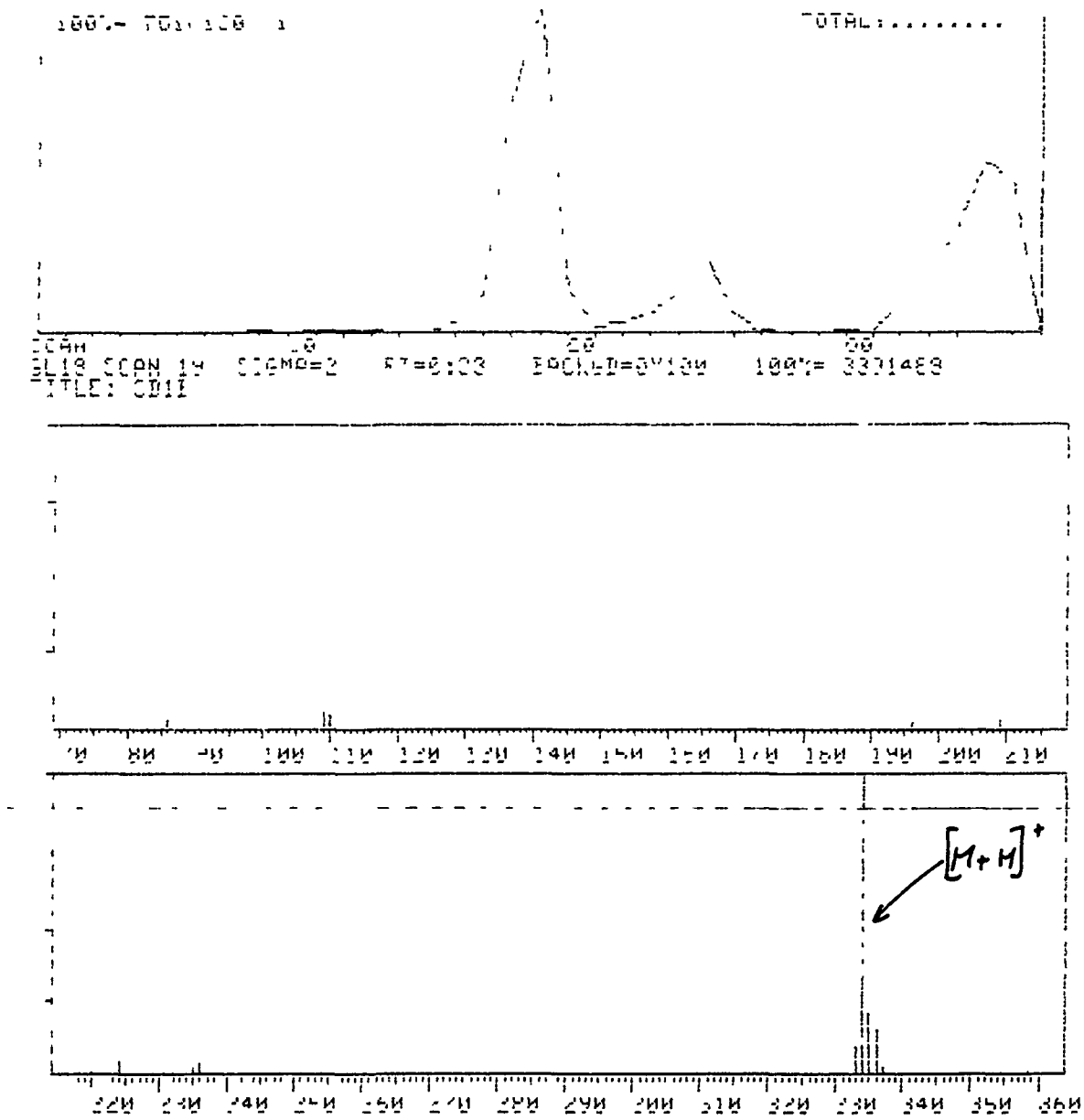


FIG. 43

GL18 SCAN 19 SIGMA=2 RT=0 33 BACKGD=0X100 100%= 3391488
TITLE SD1R

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	110 00	8 8	336 00	4 7	334 00	100 0	336 00	16 1

IN

START = 1 END = 40

TOTAL		487744
334 0		148864

#PA

ACQUISITION PARAMETER TABLE

MASS RANGES 70-550
INTEGRATION TIMES
TYPE OF RUN NON IFSC

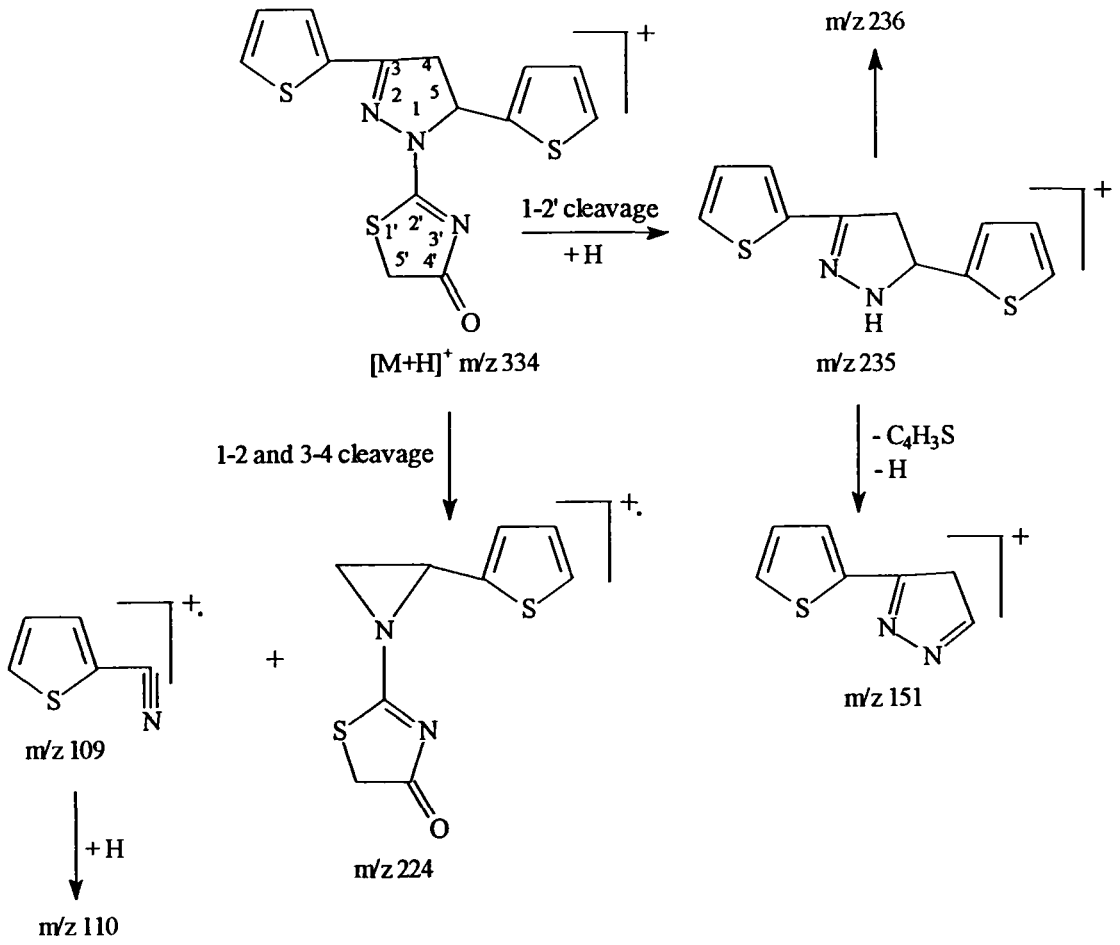

m/z 236
1-2' cleavage
+H
[M+H]+ m/z 334
m/z 235
1-2 and 3-4 cleavage
- C4H3S
- H
m/z 151
m/z 109
+H
m/z 110
m/z 224

CHART - 14

SD_{1A} with chloroacetic acid thereby forming thiazolinone ring. The main fragment ion peaks observed at m/z 224 $[(M+H) - C_5H_4NS]^+$ and m/z 110 $[(M+1) - C_9H_8N_2OS_2]^+$ were arised by the cleavage of 1-2 and 3-4 bonds of pyrazoline ring. The mode of fragmentation is shown in **CHART-14**. The ^{1}H-NMR (**FIG. 44**) and ^{13}C-NMR (**FIG. 45**) spectra of SD_{1B} dissolved in acetone-d_6 showed signals as assigned in **TABLE-15**. The assignments of all ^{1}H-NMR and ^{13}C-NMR signals to individual H- and C-atoms have been performed on the basis of typical chemical shift values, multiplicity, relative integrations and by comparison of the spectral data of SD_{1A} (19) (**TABLE-14**). The two double doublets at δ3.67 (J=17.85 Hz, J=3.51 Hz) and δ4.23 (J=17.85 Hz, J=10.84 Hz) were assigned to H-4eq and H-4ax protons respectively. A double doublet at δ6.16 (J=3.51 Hz, J=10.84 Hz) was attributed to proton for H-5ax. Thus, the coupling constants showed that two diasterotopic hydrogens at C-4 are anti and synperiplanar with C-5 hydrogen. The signal corresponding to NH_2 protons at δ7.12, 7.40 in SD_{1A} (19) (**TABLE-14**) has disappeared in the ^{1}H-NMR spectrum of SD_{1B}, showing that NH_2 group was involved in the formation of the thiazolinone ring. The formation of the ring has also been supported by the appearance of new signal at δ3.85 corresponding to methylene protons of thiazolinone ring. The ^{13}C-NMR spectrum showed a signal of δ187.01 (C-4') for carbonyl carbon. The signal corresponding to C=S group did not appear and in place other signals at δ178.64 (C-2'), 39.30 (C-5') appeared. The aromatic carbons signals were assigned as shown in the **TABLE-15**.

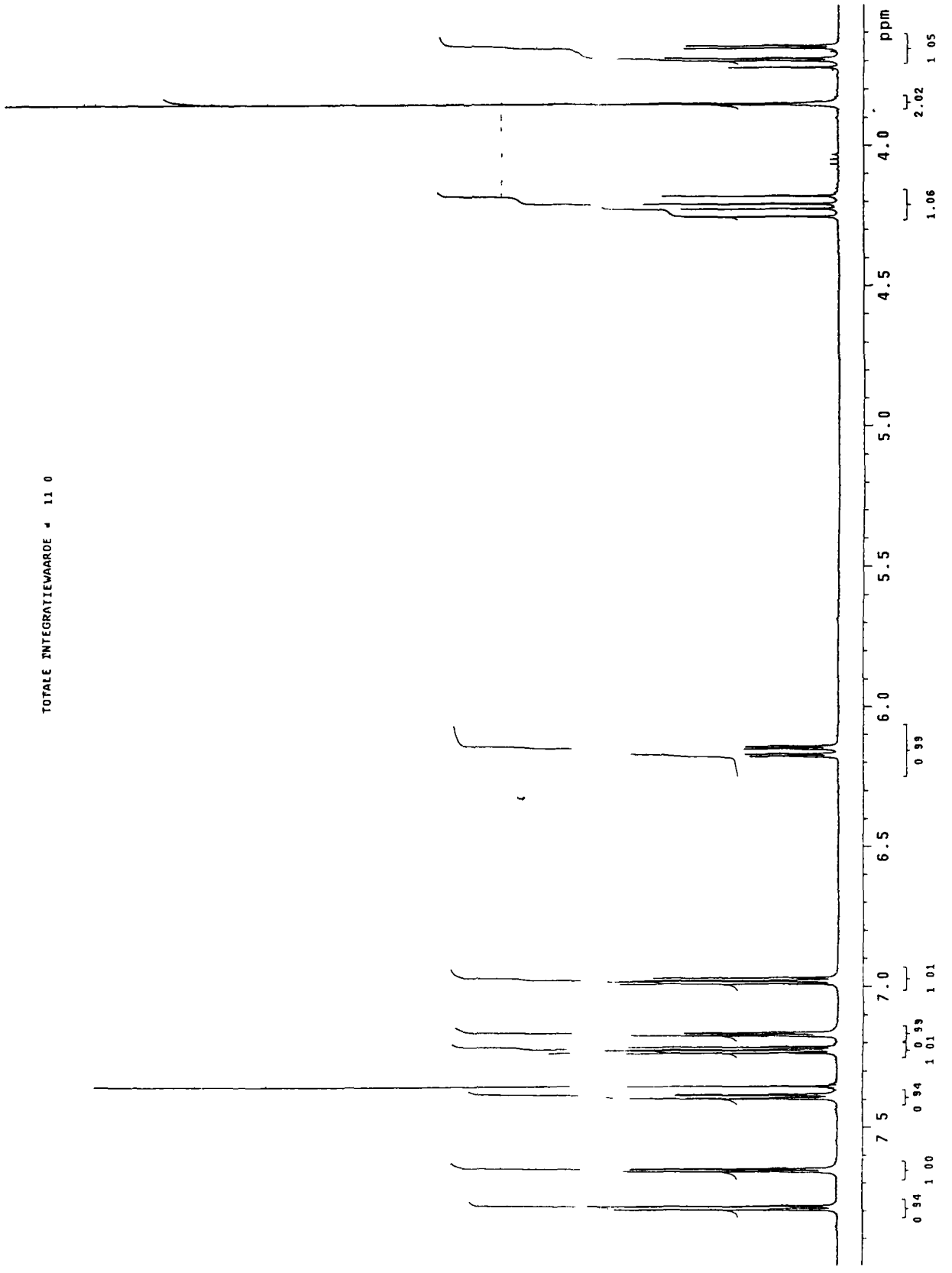

TOTALE INTEGRATIEWAARDE = 11 0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
ppm
0.94
1.00
0.94
1.01
0.99
1.01
0.99
1.06
2.02
1.05

FIG. 44

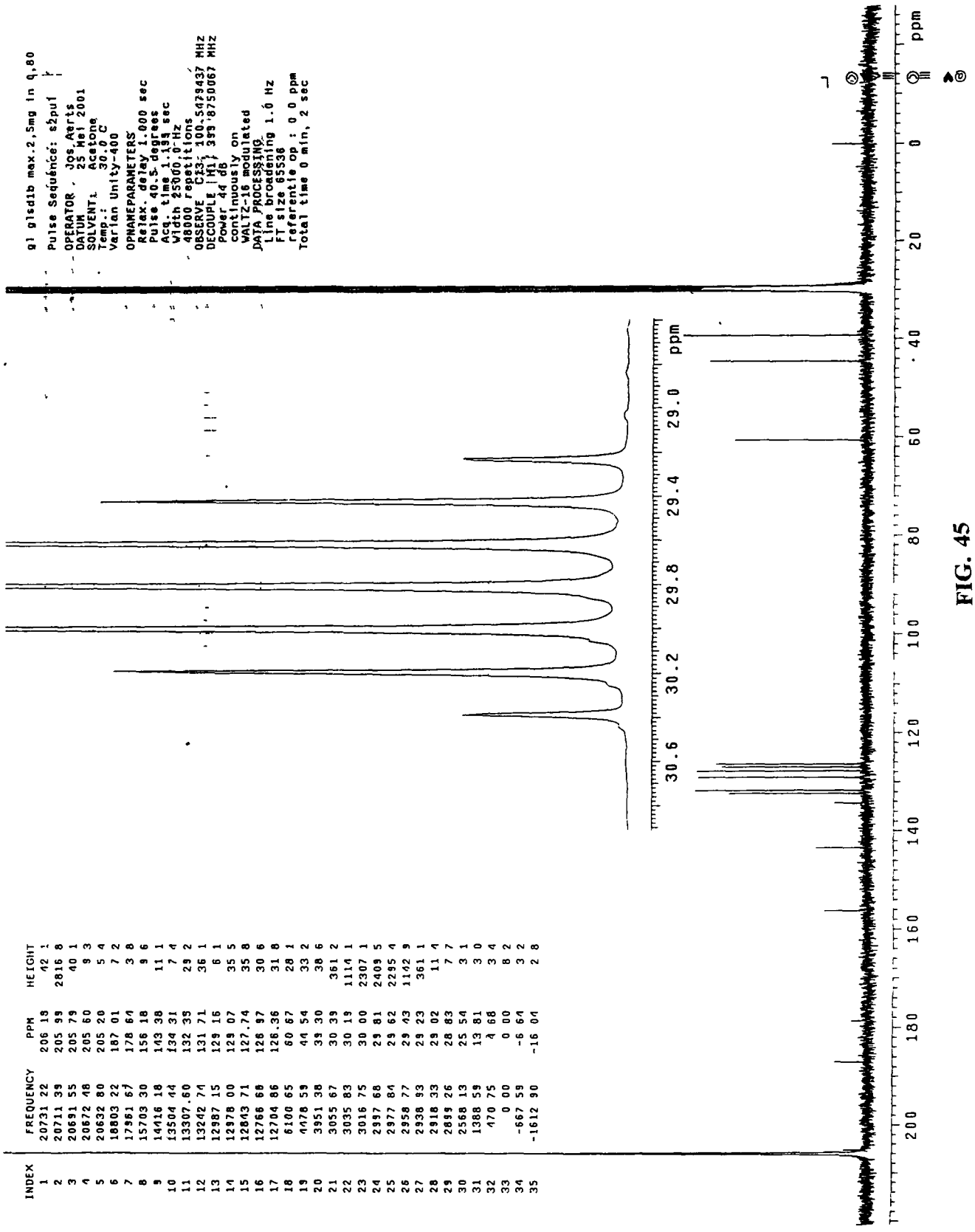
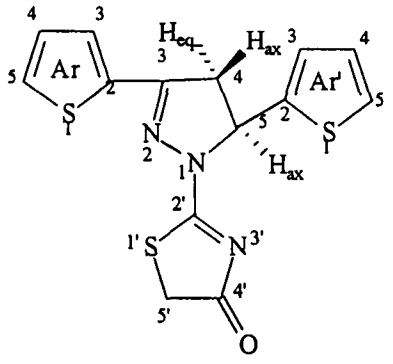

gl glsdib max.2,5mg in q,80
Pulse Sequence: s2pul
OPERATOR , Jos Aerts
DATUM 25 Mei 2001
SOLVENT: Acetone
Temp.: 30.0 C
Varian Unity-400
OPNAMEPARAMETERS
Relax. delay 1.000 sec
Pulse 40.5 degrees
Acq. time 1.134 sec
Width 25000.0 Hz
48000 repetitions
OBSERVE C13, 100.5429437 MHz
DECOUPLE H1, 399.8750067 MHz
Power 44 db
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
reference op : 0.0 ppm
Total time 0 min, 2 sec
INDEX FREQUENCY PPM HEIGHT
1 20731.22 206.13 42.1
2 20711.39 205.99 2816.8
3 20691.55 205.79 40.1
4 20672.48 205.60 9.3
5 20632.80 205.20 5.4
6 18803.22 187.01 7.2
7 17361.67 178.64 3.8
8 15703.30 156.18 9.6
9 14416.18 143.38 11.1
10 13504.44 134.31 7.4
11 13307.60 132.33 29.2
12 13242.74 131.71 36.1
13 12987.15 129.16 6.1
14 12978.00 129.07 35.5
15 12843.71 127.74 35.8
16 12766.68 126.97 30.6
17 12704.86 126.36 31.8
18 6100.65 60.67 28.1
19 4478.59 44.54 33.2
20 3951.38 39.30 38.6
21 3055.67 30.39 361.2
22 3035.83 30.19 1114.1
23 3016.75 30.00 2307.1
24 2997.68 29.81 2405.5
25 2977.84 29.62 2295.4
26 2958.77 29.43 1142.9
27 2938.93 29.23 361.1
28 2918.33 29.02 11.4
29 2899.26 28.83 7.7
30 2568.13 25.54 3.1
31 1388.59 13.81 3.0
32 470.75 4.68 3.4
33 0.00 0.00 8.2
34 -667.59 -6.64 3.2
35 -1612.90 -16.04 2.8
30.6
30.2
29.8
29.4
29.0
ppm
200
180
160
140
120
100
80
60
40
20
0
ppm

FIG. 45

TABLE -15 : ^{1}H-NMR and ^{13}C-NMR spectral data of SD_{1B} (20)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)	C-nr	δ (ppm)
4eq	3.67	1H	dd	$J_{4eq,4qx}$=17.85, $J_{4eq,5ax}$=3.51	3	156.18
4ax	4.23	1H	dd	$J_{4eq,4ax}$=17.85, $J_{4ax,5ax}$=10.84	4	44.54
5ax	6.16	1H	dd	$J_{4eq,5ax}$=3.51, $J_{4ax,5ax}$=10.84	5	60.67
5'	3.85	2H	s	–	2'	178.64
Ar-3	7.17	1H	ddd	$J_{Ar-3,4}$=3.66, $J_{Ar-3,5}$=1.22	4'	187.01
				$J_{Ar-3,5ax}$=0.77		
Ar-4	6.99	1H	dd	$J_{Ar-3,4}$=3.66, $J_{Ar-4,5}$=5.04	5'	39.30
Ar-5	7.39	1H	dd	$J_{Ar-3,5}$=1.22, $J_{Ar-4,5}$=5.04	Ar + Ar'	126.36-143.38
Ar'-3	7.65	1H	dd	$J_{Ar'-3,4}$=3.66, $J_{Ar'-3,5}$=1.22		
Ar'-4	7.24	1H	dd	$J_{Ar'-3,4}$=3.66, $J_{Ar'-4,5}$=5.04		
Ar'-5	7.79	1H	dd	$J_{Ar'-4,5}$=5.04, $J_{Ar'-3,5}$=1.22		

On the basis of these facts, SD_{1B} was characterized as *2-[3,5-bis(2-thienyl)-2-pyrazoline-1-yl]thiazolin-4-one (20).*



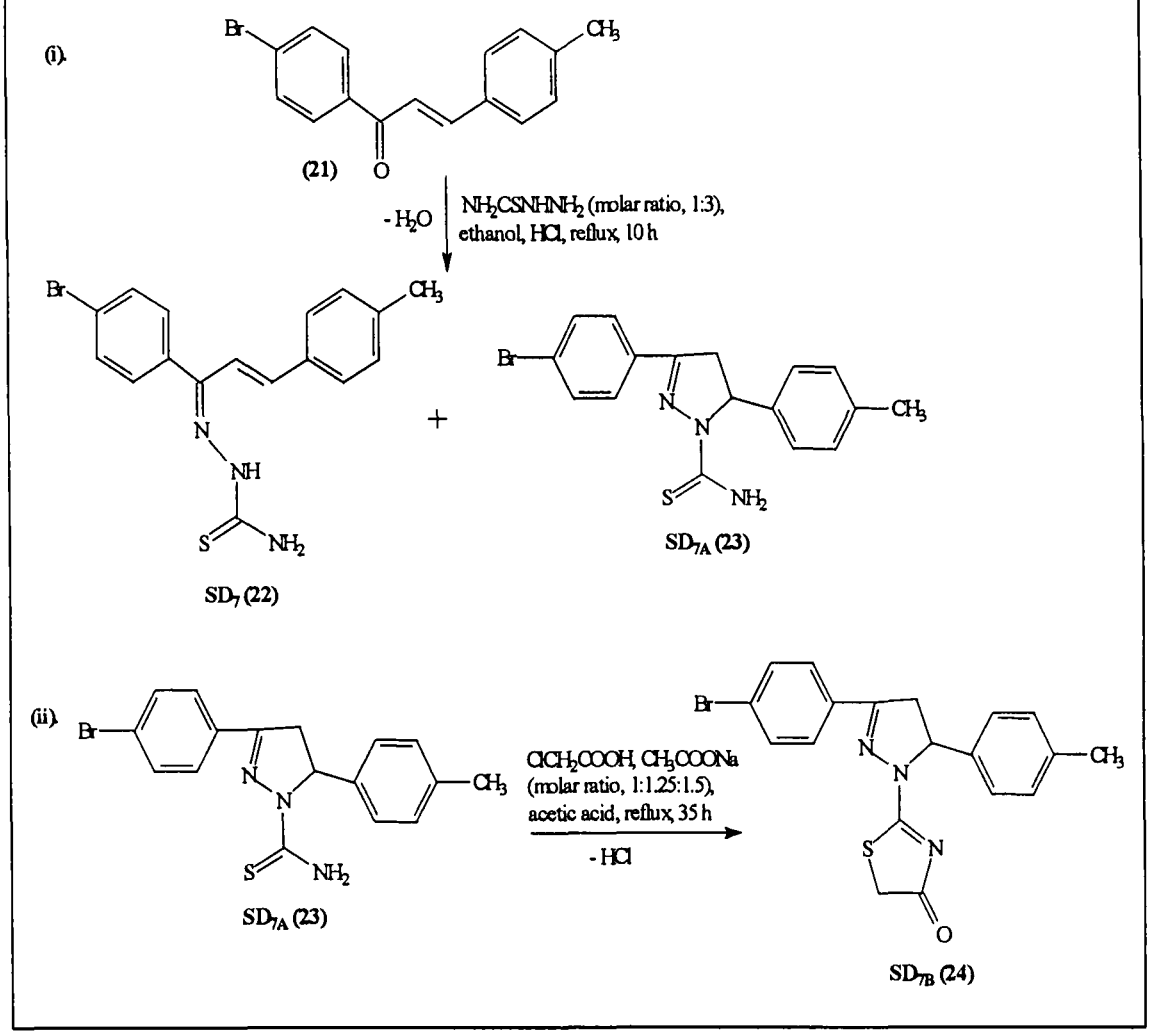
SD_{1B} (20)

Synthesis of 2-[3-(4-bromophenyl)-5-(4-methylphenyl)-2-pyrazolin-1-yl]thiazolin-4-one SD_{7B} (24) from 4-bromophenyl-4-methylphenyl-2-propen-1-one (21) via 2-[3-(4-bromophenyl)-5-(4-methylphenyl)-2-pyrazolin-1-yl]thiocarboxamide SD_{7A} (23) using chloroacetic acid in the presence of sodium acetate

The compound SD_{7B} (24) was prepared as mentioned above. The pyrazolinyl thiacarboxamide SD_{7A} (23) was first prepared by refluxing a solution of bromomethyl chalcone (21) and thiosemicarbazide (molar ratio, 1:3) in absolute alcohol in the presence of conc. HCl, for 10 h. After completion of the reaction, the reaction mixture on TLC examination (silica gel 'G', benzene-ethyl acetate, 8:2 v/v) showed the presence of two spots, levelled as SD_7 and SD_{7A}. On usual work up and column chromatography followed by crystallization from benzene acetone, it yielded SD_7 as orange crystalline needles and SD_{7A} as brown crystalline needles in 14% and 66% yields. SD_{7A} was then condensed with chloroacetic acid and sodium acetate (molar ratio, 1:1.25:1.5). The cyclocondensation was carried out by refluxing the reaction mixture in freshly distilled acetic acid for 35 h. TLC examination (silica gel 'G', benzene-ethyl acetate, 8:2 v/v) of the reaction mixture showed the presence of only one spot, levelled as SD_{7B}. After usual work up and purification of the products by column chromatography over silica gel using

benzene-ethyl acetate (8:2 v/v) as eluent followed by crystallization (benzene-acetone, 9:1 v/v) yielded **SD_{7B} (24)** as dark brown crystalline needles in 55% yield.

The reaction sequence is given below :



Structure Elucidation of SD_7 (21)

It is an orange crystalline solid, m.p. 182 °C and appears brown on exposure to iodine vapours (TLC). The constitution of **SD_7** has been established by FT-IR, FAB-Mass, ^{1}H-NMR, ^{13}C-NMR spectra. IR spectrum

(KBr) displayed characteristic absorption bands at 3464 (NH), 2930 (CH), 1584 (C=N), 1478 (phenyl), 1386, 1326, 1250, 1117, 1072, 981, 867, 805, 768, 712 cm^{-1}. The FAB-MS spectrum **(FIG. 46)** **SD_7 (22)** showed $[M]^+$ ion peaks at m/z 374/376 as the base peak confirming its molecular weight 374/376. This is equal to the sum of the molecular weights of chalcone (301) and thiosemicarbazide (91) minus one molecule of water (18) which indicated the formation of thiosemicarazone by the condensation of chalcone with thiosemicarbazide. The sets of peaks were observed at m/z 340/342 $[M-H_2S]^+$ and m/z 357/359 $[M-NH_3]^+$. The mode of fragmentation is shown in **CHART-15**. The ^{1}H-NMR **(FIG. 47)** and ^{13}C-NMR **(FIG. 48)** spectra of **SD_7** dissolved in $CDCl_3$ and DMSO respectively showed signals as assigned **(TABLE-16)**. The assignments of all ^{1}H-NMR and ^{13}C-NMR signals to individual H- and C-atoms have been performed on the basis of typical chemical shift values, multiplicity, relative integrations and also by comparison with previously described thiosemicarbazone **SD_1 (18)** **(TABLE-13)**. The ^{1}H-NMR of **SD_7** showed two doublets at δ6.36 (J=16.20 Hz) and δ7.03 (J=16.20 Hz) which were assigned to C-2 and C-3 protons. The large coupling constant (J=16.20 Hz) of vicinal protons confirmed their trans dispositions. The proton at C-3 appeared at lower field (δ7.03) as compared to proton at C-2 (δ6.36) due to the deshielding effect of aryl group attached to it. A broad singlet at δ10.57 appeared for NH proton. The singlet at δ2.38 was accounted for one methyl group protons. The aromatic protons signals were observed at δ7.12-7.75. The ^{13}C-NMR spectrum showed signals at δ148.5 (C-1), δ115.70 (C-2) and δ135.50 (C-3). The signal at δ179.0 was attributed to C=S carbon. The signal at δ21.10 was assigned for methyl carbon. The aromatic carbons signals were observed at δ123.50-141.50 **(TABLE-16)**.

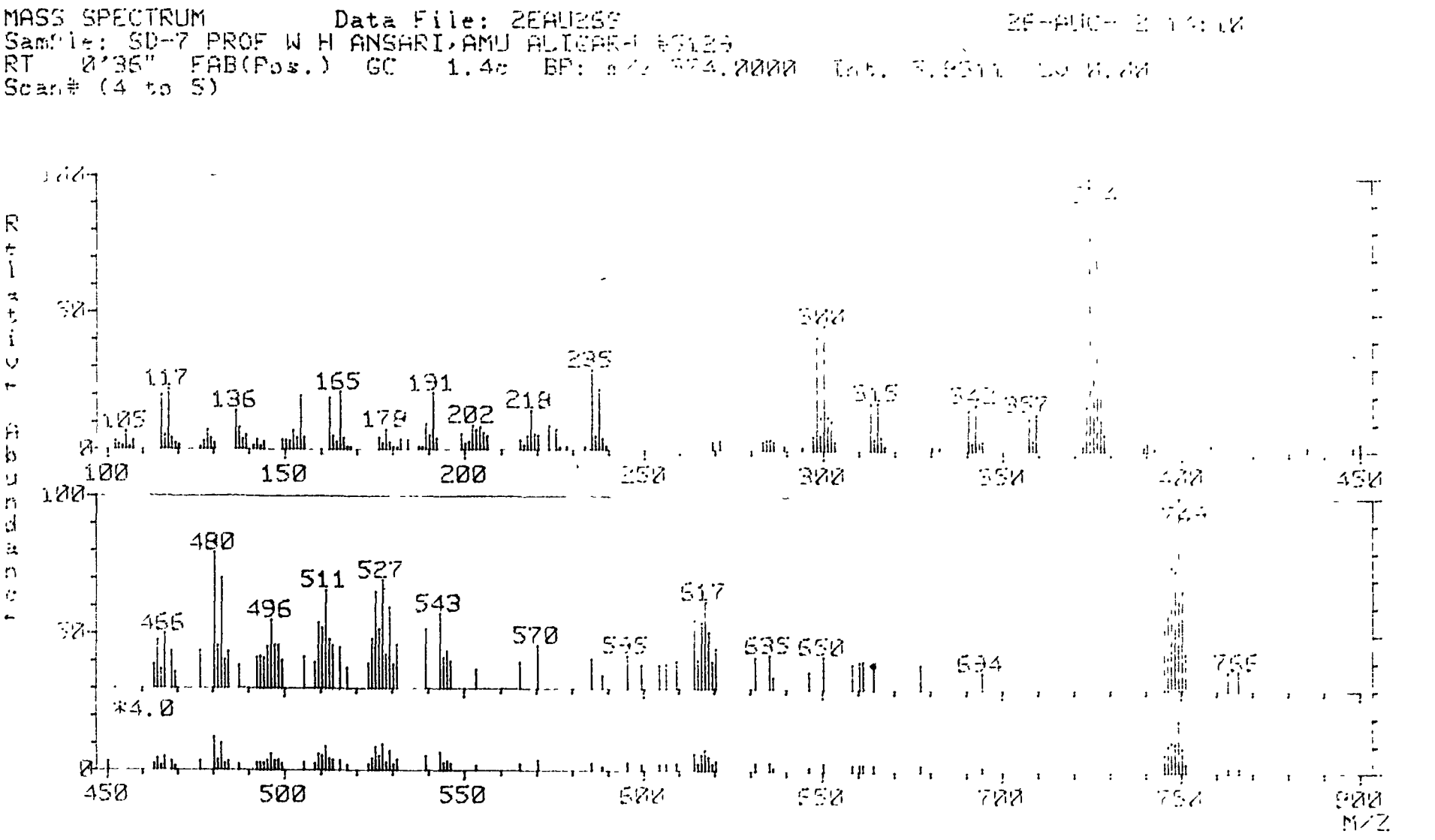

MASS SPECTRUM
Data File: ZEAL259
Sample: SD-7 PROF W H ANSARI,AMU ALIGAR-I
RT 0'35" FAB(Pos.) GC 1.4e
Scan# (4 to 5)
Relative Abundance
m/z
105
117
136
165
179
191
202
218
235
300
315
342
357
455
480
496
511
527
543
570
595
617
635
650
694
744
755
*4.0

FIG. 46

220

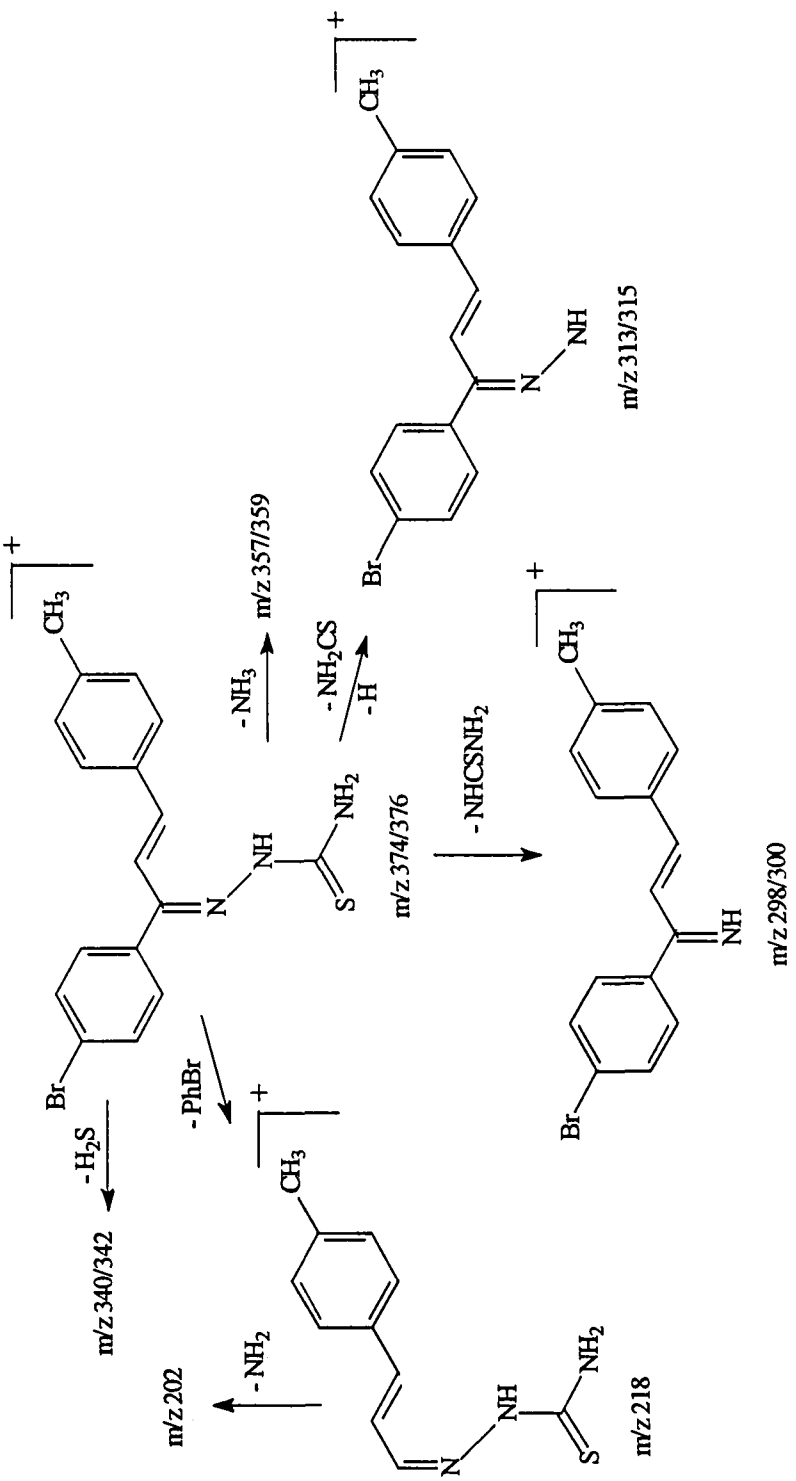

-H2S
m/z 340/342
-PhBr
-NH3
m/z 357/359
-NH2CS
-H
m/z 374/376
-NHCSNH2
m/z 313/315
m/z 298/300
-NH2
m/z 202
m/z 218

CHART - 15

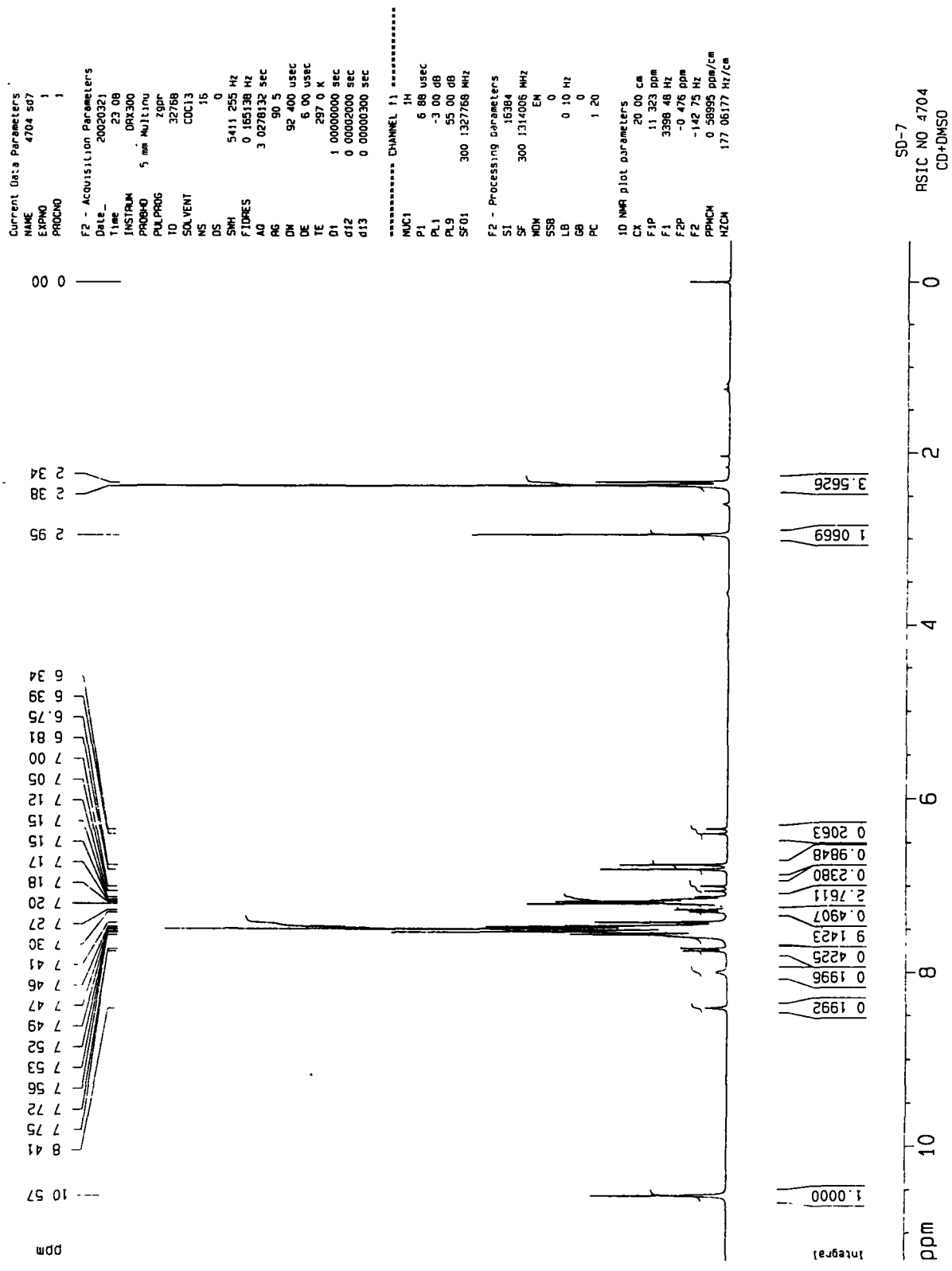
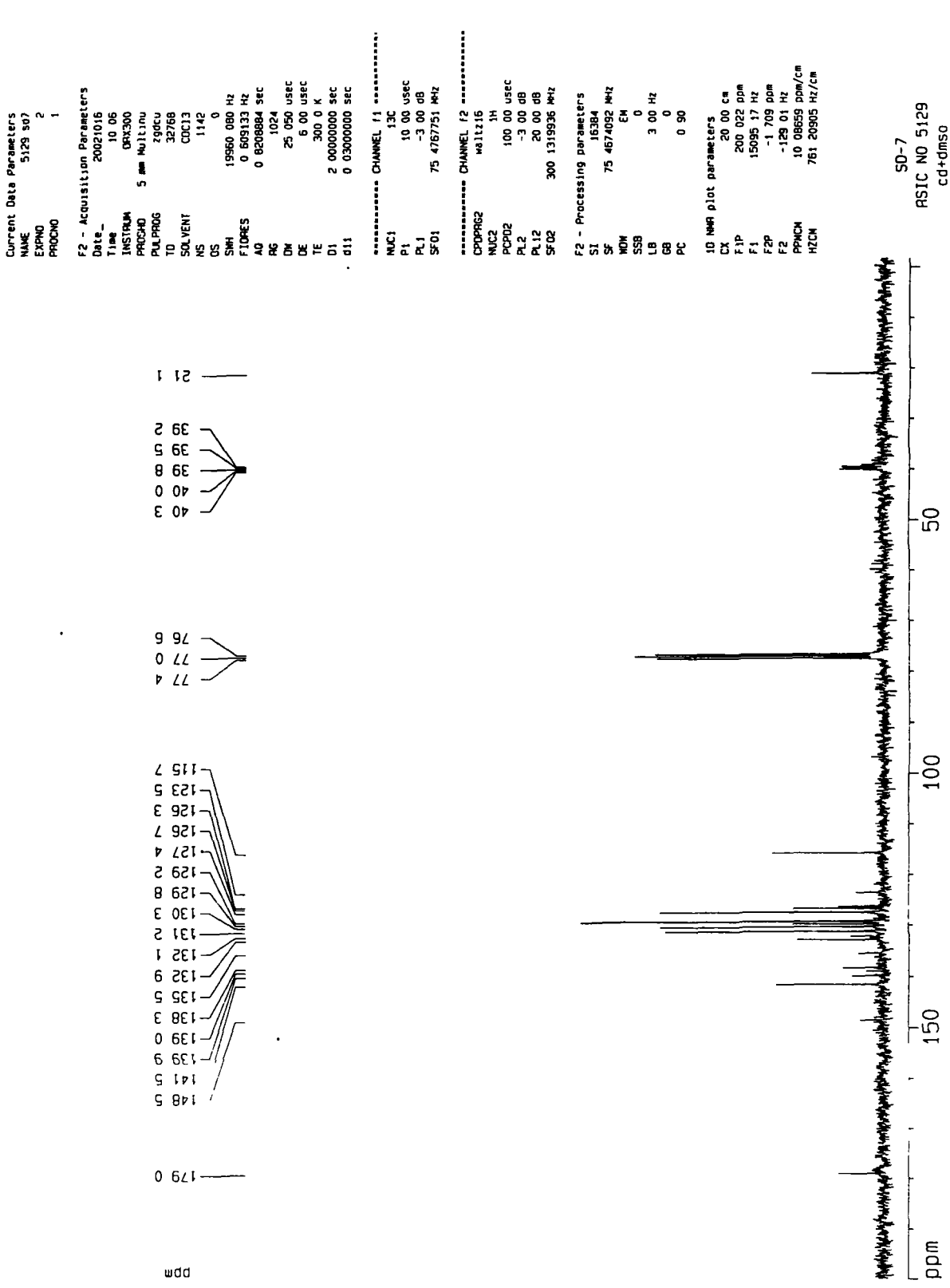


FIG. 47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PROCNO 1
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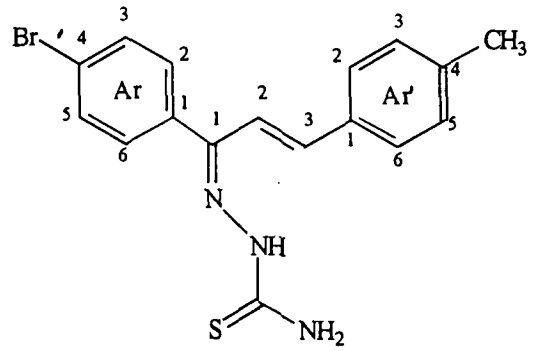
PULPROG zgdcu
TD 32768
SOLVENT CDCl3
NS 1142
DS 0
SWH 19960 080 Hz
FIDRES 0 609133 Hz
AQ 0 8208884 sec
RG 1024
DW 25 050 usec
DE 6 00 usec
TE 300 0 K
D1 2 00000000 sec
D11 0 03000000 sec
CHANNEL f1
NUC1 13C
P1 10 00 usec
PL1 -3 00 dB
SFO1 75 4767751 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100 00 usec
PL2 -3 00 dB
PL12 20 00 dB
SFO2 300 1319936 MHz
F2 - Processing parameters
SI 16384
SF 75 4674092 MHz
WDW EM
SSB 0
LB 3 00 Hz
GB 0
PC 0 90
1D NMR plot parameters
CX 20 00 cm
F1P 200 022 ppm
F1 15095 17 Hz
F2P -1 709 ppm
F2 -129 01 Hz
PPMCM 10 08659 ppm/cm
HZCM 761 20905 Hz/cm
SD-7
RSIC NO 5129
cd+dmso
ppm
50
100
150
179 0
148 5
141 5
139 9
139 0
138 3
135 5
132 9
132 1
131 2
130 3
129 8
129 2
127 4
126 7
126 3
123 5
115 7
77 4
77 0
76 6
40 3
40 0
39 8
39 5
39 2
21 1

FIG. 48

TABLE -16 : ^{1}H-NMR and ^{13}C-NMR spectral data of SD_7 (22)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)	C-nr	δ (ppm)
2	6.36	1H	d	$J_{2,3}$=16.20	1	148.50
3	7.03	1H	d	$J_{2,3}$=16.20	2	115.70
NH_2	8.41	2H	s	–	3	135.50
NH	10.57	1H	s	–	C=S	179.0
Ar-CH_3	2.38	3H	s	–	Ar-CH_3	21.10
2 x Ar	7.12-7.75	8H	br m	–	2 x Ar	123.50-141.50

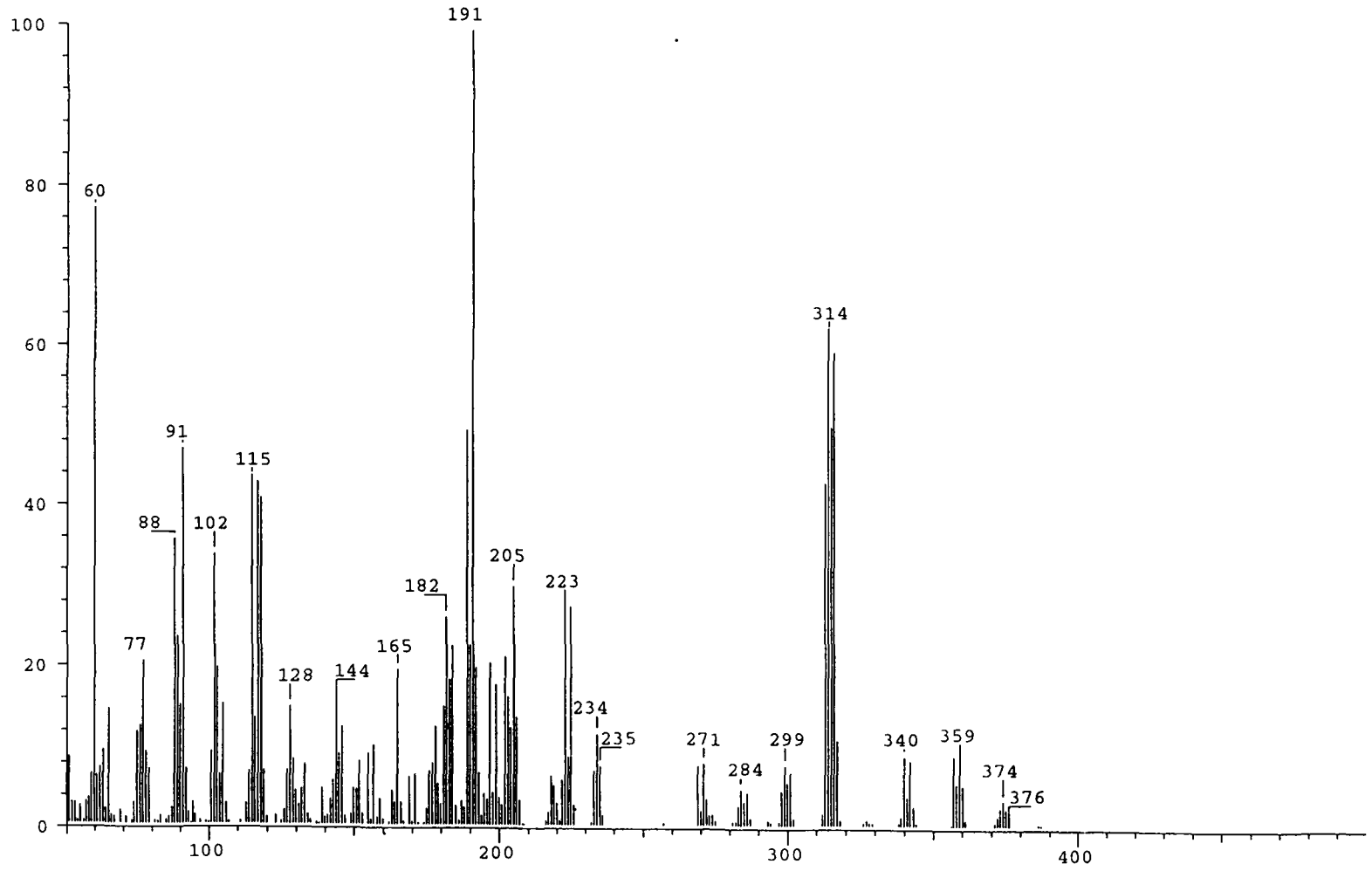
On the basis of above spectral evidence, the product **SD_7 (22)** was characterized as *N^1-[1-(4-bromophenyl)-3-(4-methylphenyl)-2-propen-1-ylidene] thiosemicarbazide (22).*



SD_7 (22)

Structure Elucidation of SD_{7A} (23)

It is a brown needles shaped crystalline solid,m.p. 200 °C and appears brown on exposure to iodine vapours (TLC). The structure of **SD_{7A}** has been fully established by FT-IR, EI-MS, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum (KBr) showed characteristic absorption bands at 3380 (NH), 2970 (CH), 1590 (C=N), 1535, 1480 (phenyl), 1330, 1115 (C=S), 1075 (C-N) cm^{-1}. The EI-MS spectrum **(FIG. 49)** of **SD_{7A}** showed a set of peaks at m/z 374/ 376 $[M]^+$, confirming its molecular weight 374/376. This is equal to the sum of the molecular weights of the chalcone **(21)** (301) and thiosemicarbazide (91) minus one molecule of water (18) which indicated the condensation has occurred between the chalcone **(21)** and thiosemicarbazide. The set of peaks at m/z 357/359 $[M\text{-}NH_3]^+$ appeared by the loss of ammonia and an another set of peaks at m/z 340/342 $[M\text{-}H_2S]^+$ due to the loss of H_2S from the molecular ion. The set of peaks at m/z 314/316 $[M\text{-}CSNH_2]^+$ were observed by the cleavage of N–C bond. The mode of fragmentation is shown in **(CHART-16)**. The ^{1}H-NMR **(FIG. 50)** and ^{13}C-NMR **(FIG. 51)** dessolved in $CDCl_3$ showed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Samp: A
Oper: Dr. RAZA
Base: 190.89
Study : ROUTINE ANALYSIS
Masses: 49.98 > 499.97
Scans : 1 > 146
Client:
#Peaks: 293
Scan 62 @ 0.59 min (EI +Q1MS LMR UP LR)
2 9E+06
100
80
60
40
20
0
100
200
300
400
191
60
314
91
115
88
102
205
223
182
77
165
128
144
234
235
271
299
340
359
284
374
376

FIG. 49

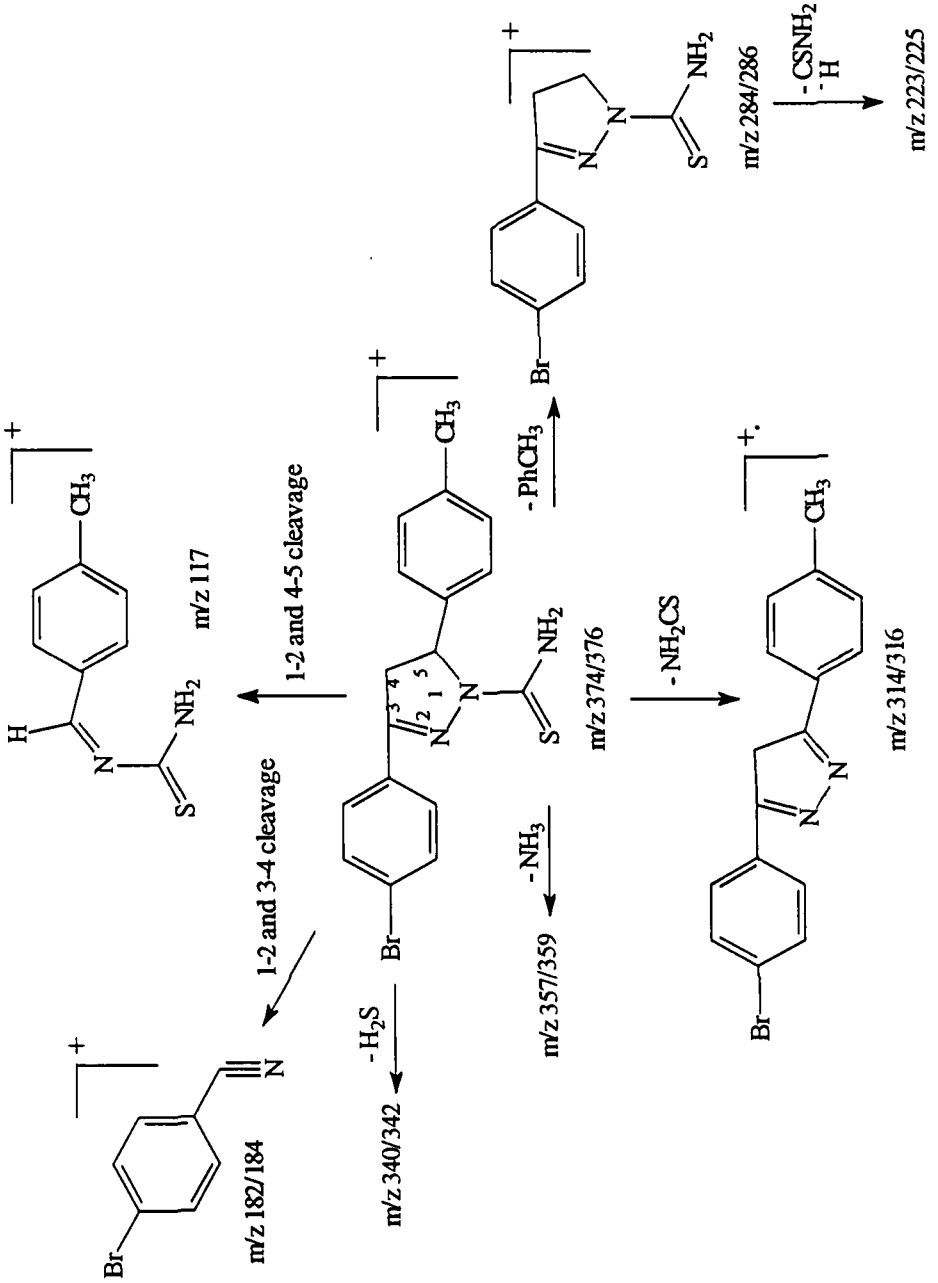
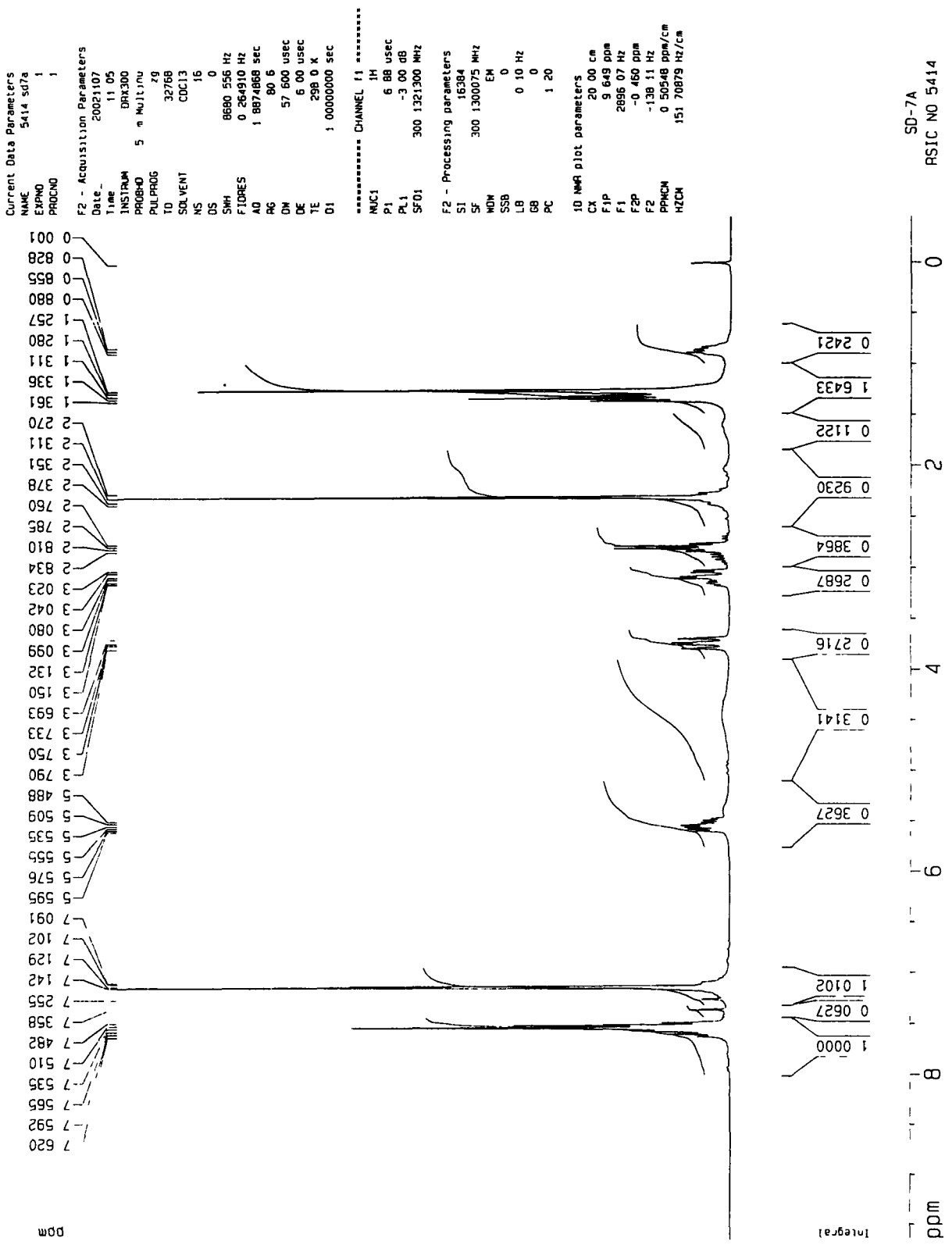

m/z 117
1-2 and 4-5 cleavage
1-2 and 3-4 cleavage
m/z 182/184
-H2S
m/z 340/342
-NH3
m/z 357/359
-PhCH3
m/z 374/376
-NH2CS
m/z 314/316
m/z 284/286
-CSNH2
H
m/z 223/225

CHART - 16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PROCNO 1
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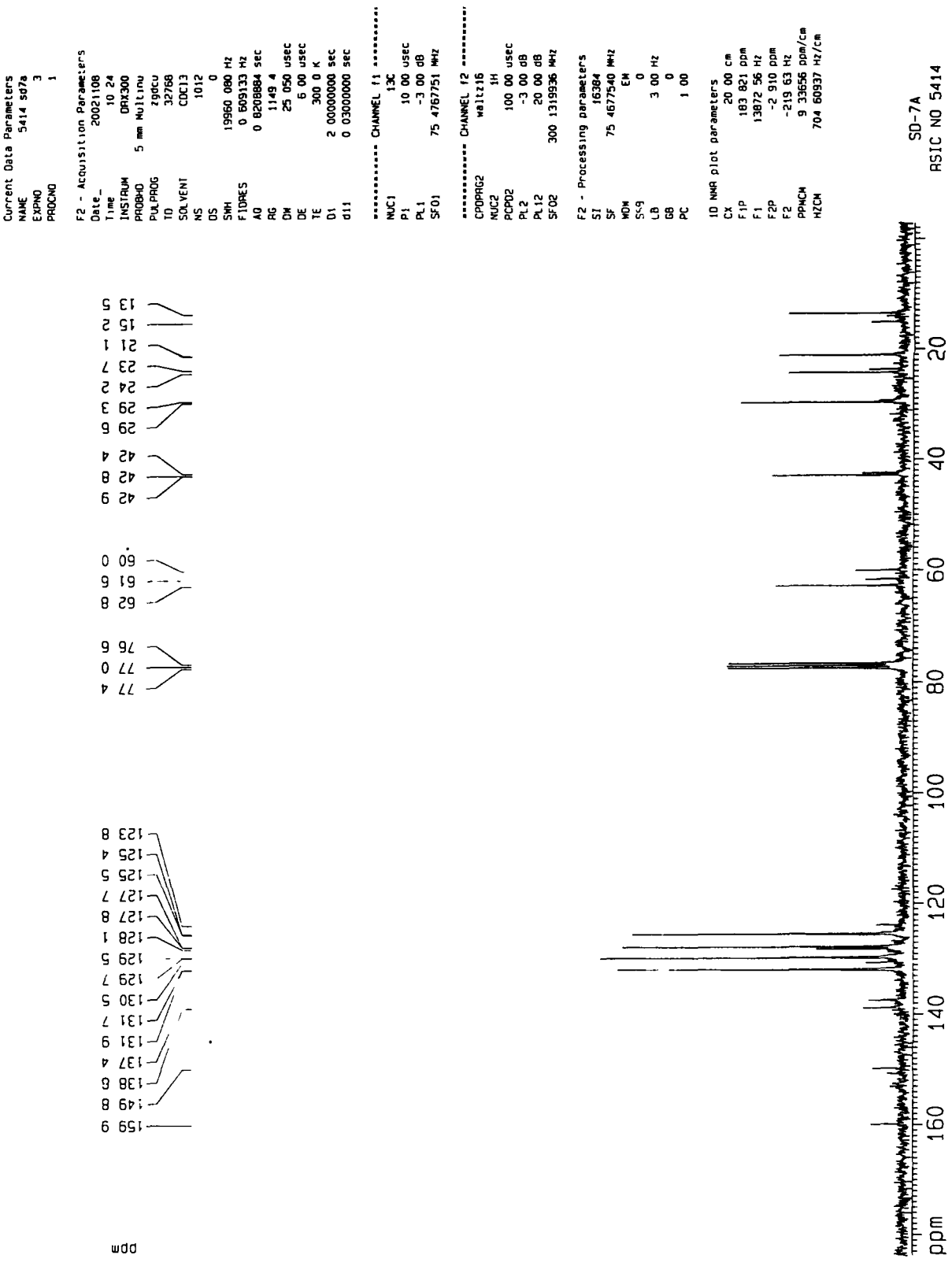
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 16
DS 0
SWH 8680 556 Hz
FIDRES 0 264910 Hz
AQ 1 8874868 sec
RG 80 6
DW 57 600 usec
DE 6 00 usec
TE 298 0 K
D1 1 00000000 sec
CHANNEL f1
NUC1 1H
P1 6 88 usec
PL1 -3 00 dB
SFO1 300 1321300 MHz
F2 - Processing parameters
SI 16384
SF 300 1300075 MHz
WDW EM
SSB 0
LB 0 10 Hz
GB 0
PC 1 20
1D NMR plot parameters
CX 20 00 cm
F1P 9 649 ppm
F1 2896 07 Hz
F2P -0 460 ppm
F2 -138 11 Hz
PPMCM 0 50548 ppm/cm
HZCM 151 70879 Hz/cm
SD-7A
RSIC NO 5414
ppm
Integral

FIG. 50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PROCNO 1
F2 - Acquisition Parameters
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Time 10 24
INSTRUM DRX300
PROBHD 5 mm Multinu
PULPROG zgdcu
TD 32768
SOLVENT CDCl3
NS 1012
DS 0
SWH 19960 080 Hz
FIDRES 0 609133 Hz
AQ 0 8208884 sec
RG 1149 4
DW 25 050 usec
DE 6 00 usec
TE 300 0 K
D1 2 00000000 sec
d11 0 03000000 sec
CHANNEL f1
NUC1 13C
P1 10 00 usec
PL1 -3 00 dB
SF01 75 4767751 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100 00 usec
PL2 -3 00 dB
PL12 20 00 dB
SF02 300 1319936 MHz
F2 - Processing parameters
SI 16384
SF 75 4677540 MHz
WDW EM
SSB 0
LB 3 00 Hz
GB 0
PC 1 00
1D NMR plot parameters
CX 20 00 cm
F1P 183 821 ppm
F1 13872 56 Hz
F2P -2 910 ppm
F2 -219 63 Hz
PPMCM 9 33656 ppm/cm
HZCM 704 60937 Hz/cm
SD-7A
RSIC NO 5414
ppm
20
40
60
80
100
120
140
160
77 4
77 0
76 6
62 8
61 6
60 0
42 9
42 8
42 4
29 6
29 3
24 2
23 7
21 1
15 2
13 5
159 9
149 8
138 6
137 4
131 9
131 7
130 5
129 7
129 5
128 1
127 8
127 7
125 5
125 4
123 8

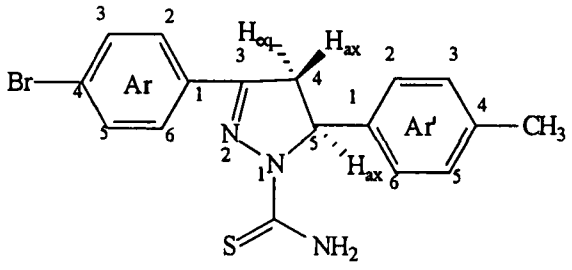
FIG. 51

TABLE -17 : ^{1}H-NMR and ^{13}C-NMR spectral data of SD_{7A} (23)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)	C-nr	δ (ppm)
4eq	3.08	1H	dd	$J_{4eq,4ax}$=17.10, $J_{4eq,5ax}$=5.70	3	159.90
4ax	3.75	1H	dd	$J_{4eq,4ax}$=17.10, $J_{4ax,5ax}$=12.0	4	42.80
5ax	5.57	1H	dd	$J_{4eq,5ax}$=5.70, $J_{4eq,5ax}$=12.0	5	61.60
NH_2	7.36	2H	s	–	C=S	not appeared
Ar-CH_3	2.35	3H	s	–	Ar-CH_3	23.70
2 x Ar	7.09-7.62	8H	br m	–	2 x Ar	123.80-138.80

signals as assigned **(TABLE-17)**. The assignments of all ^{1}H- and ^{13}C-NMR signals to specific H- and C-atoms have been performed on the basis of typical chemical shift values, multiplicity, relative integrations and also by comparison with the spectral data of $\mathbf{SD_7}$ **(22) (TABLE-16)** and $\mathbf{SD_{1A}}$**(19) (TABLE-14).** The two double doublets at δ3.08 (J=17.10Hz, J=5.70Hz) and δ3.75 (J=17.10Hz, J=12.0Hz) were assigned to H-4eq and H-4ax respectively. The another double doublet at δ5.57 (J=5.70Hz, J=12.0Hz) was attributed to the proton of H-5ax. These coupling constants showed that the two diastereotopic hydrogen atoms at C-4 are anti and synperiplanar with C-5 hydrogen. A singlet was also observed at δ7.36 for NH_2 protons. The aromatic protons signals at δ7.09-7.62 for two benzene rings were accounted for eight protons **(TABLE-17)**. The ^{13}C-NMR spectrum showed signals at δ159.90 (C-3), 42.80 (C-4), 61.60 (C-5), 23.70 (C-Ar-CH_3) and the aromatic carbons signals at δ123.80-138.80.

Based on the above spectral evidence, $\mathbf{SD_{7A}}$ was characterized as *2-[3-(4-bromophenyl)-5-(4-methylphenyl)-2-pyrazolin-1-yl]thiocarboxamide* ***(23)***.



SD_{7A} (23)

Structure Elucidation SD_{7B}(24)

It is a dark brown needle shaped crystalline solid, m.p. 230 °C and appears brown on exposure to iodine vapours (TLC). The constitution of $\mathbf{SD_{7B}}$ has been confirmed by FT-IR, EI-MS, ^{1}H-NMR and ^{13}C-NMR spectra. The IR

spectrum (KBr) of SD_{7B} displayed characteristic absorption bands at 2964 (CH), 1699 (C=O), 1593 (C=N), 1538 (phenyl), 1486 (-S-CH_2), 1389, 1331, 1211, 1111, 1067, 1006, 946, 867, 820, 707 cm^{-1}. The EI-MS spectrum **(FIG. 52)** showed a set of peaks $[M+1]^+$ at m/z 415/417, confirming its molecular weight 414/416. This is equal to the sum of the molecular weights of SD_{7A} (374) and chloroacetic acid (94) minus one molecule each of water (18) and HCl (36). This indicated the formation of thiazolinone ring by the cyclocondensation of SD_{7A} with chloroacetic acid. The mode of fragmentation is shown in **CHART-17.** The ^{1}H-NMR **(FIG. 53)** and ^{13}C-NMR **(FIG. 54)** spectra of SD_{7B} dissolved in $CDCl_3$ and DMSO showed signals as assigned in **TABLE-18.** The assignments of all ^{1}H-NMR and ^{13}C-NMR signals to specific H- and C-atoms have been performed on the basis of typical chemical shift values, multiplicity, relative integratitons and by comparison of spectral data with that of compounds SD_{1B} **(20) (TABLE-15)** and SD_{7A} **(23) (TABLE-17)**. The signal corresponding to NH_2 protons at δ7.36 in SD_{7A} **(TABLE-17)** has disappeared in the ^{1}H-NMR spectrum of SD_{7B} and a new signal appeared at δ3.83 corresponding to methylene protons, suggesting the formation of a thiazolinone ring. The aromatic protons signals for benzene rings containing eight protons were observed at δ7.11-7.68 **(TABLE-18)**. The ^{13}C-NMR spectrum showed a new signal at δ187.42 for carbonyl carbon of the thiazolinone ring. The other carbons signals observed at δ158.52 (C-3), 43.21 (C-4), 63.88 (C-5), 178.27 (C-2'), 38.96 (C-5'), 21.00 (C-Ar-CH_3) and the aromatic carbons signals at δ125.69-138.14 were observed **(TABLE-18).**

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Samp: D
Oper: Dr. RAZA
Base: 116.73
Study : ROUTINE ANALYSIS
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Scans : 1 > 149
Client:
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7.2E+05

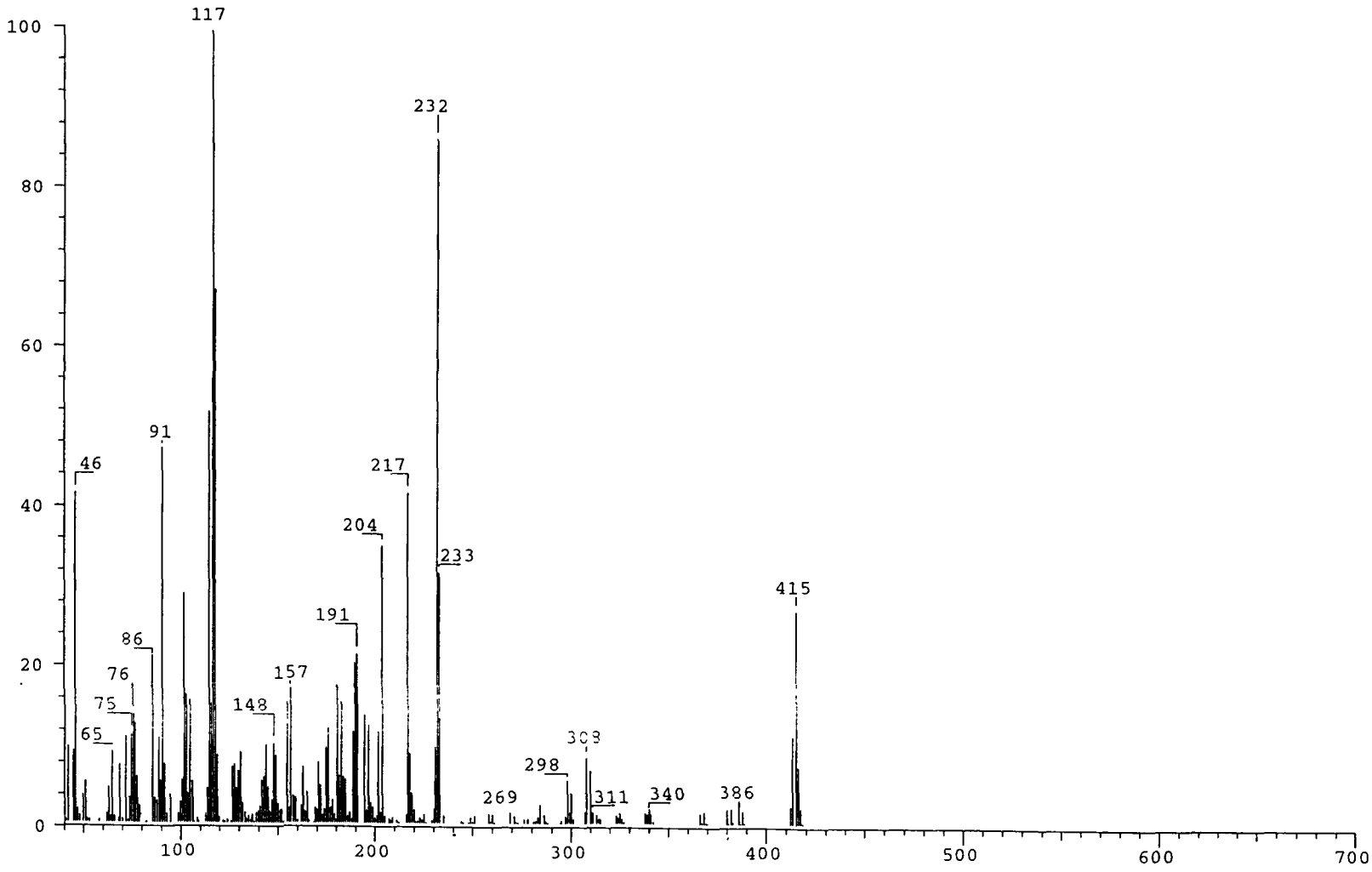
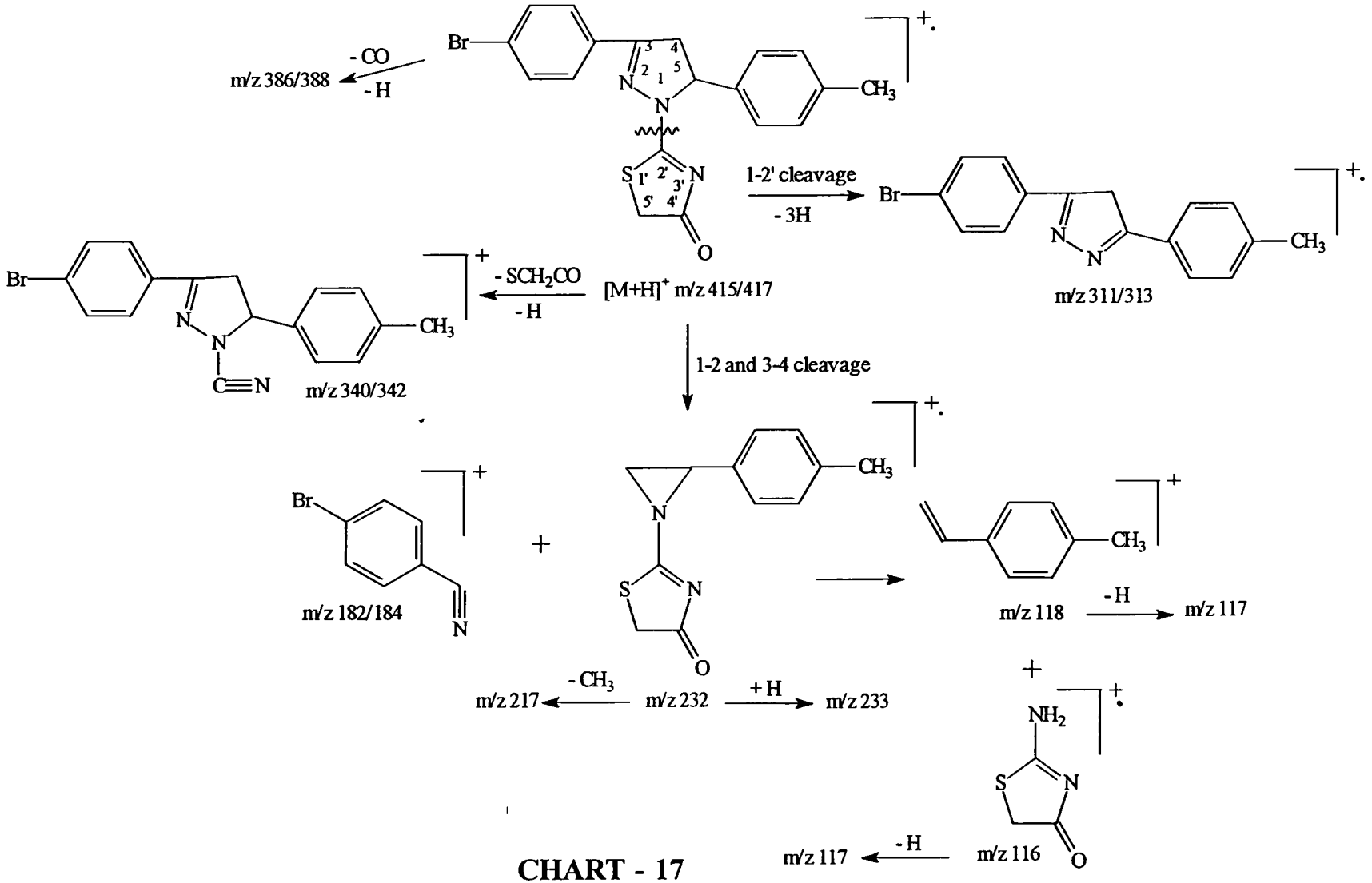


FIG. 52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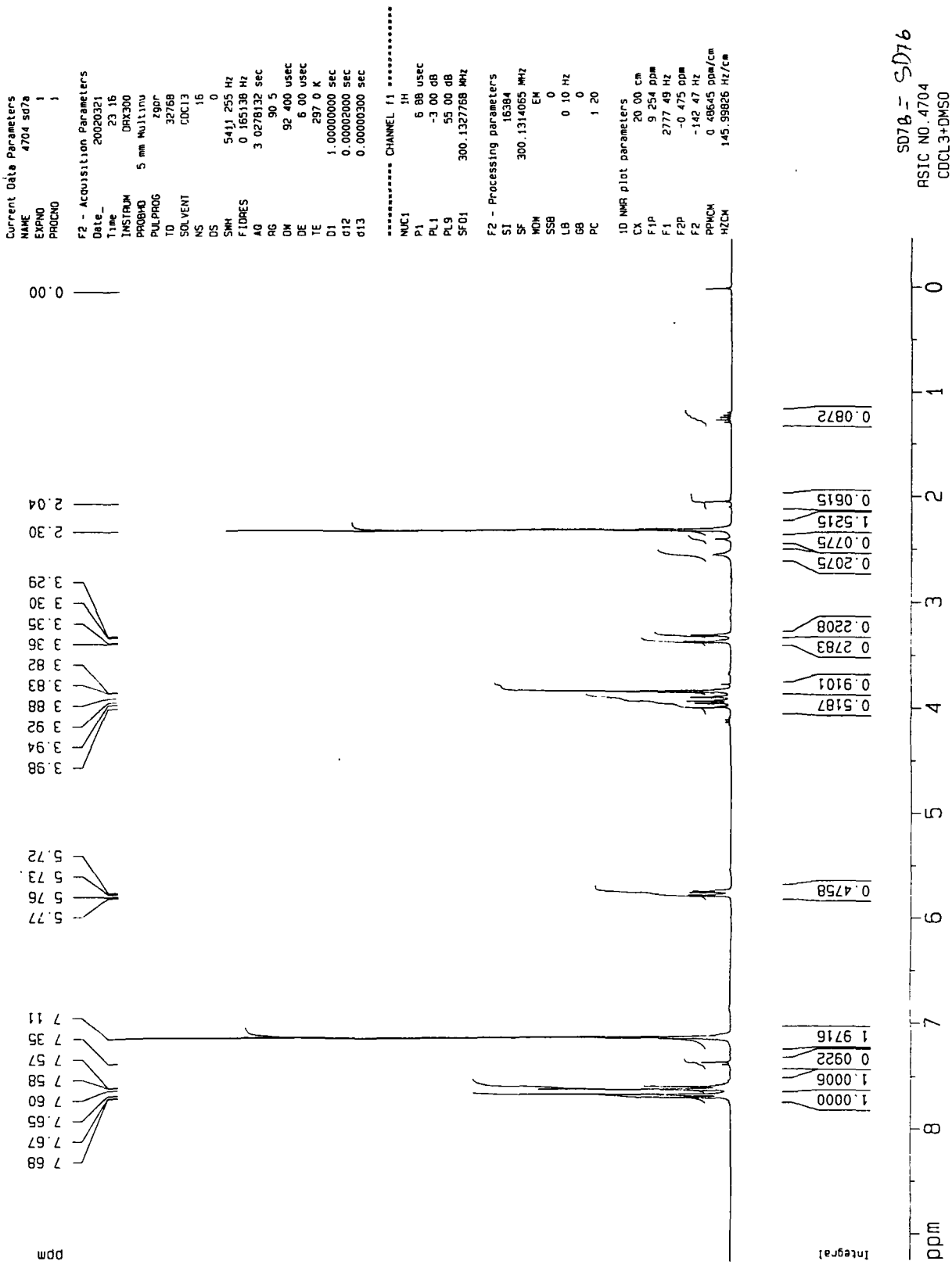
- H
m/z 386/388
Br
CH3
1-2' cleavage
- 3H
m/z 311/313
- SCH2CO
- H
[M+H]+ m/z 415/417
C≡N
m/z 340/342
1-2 and 3-4 cleavage
m/z 182/184
m/z 118
- H
m/z 117
- CH3
m/z 217
m/z 232
+ H
m/z 233
NH2
m/z 116
- H
m/z 117

CHART - 17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PROCNO 1
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TD 32768
SOLVENT CDCl3
NS 16
DS 0
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FIDRES 0 165138 Hz
AQ 3 0278132 sec
RG 90 5
DW 92 400 usec
DE 6 00 usec
TE 297 0 K
D1 1 00000000 sec
d12 0 00002000 sec
d13 0 00000300 sec
CHANNEL f1
NUC1 1H
P1 6 88 usec
PL1 -3 00 dB
PL9 55 00 dB
SFO1 300 1327768 MHz
F2 - Processing parameters
SI 16384
SF 300 1314065 MHz
WDW EM
SSB 0
LB 0 10 Hz
GB 0
PC 1 20
1D NMR plot parameters
CX 20 00 cm
F1P 9 254 ppm
F1 2777 49 Hz
F2P -0 475 ppm
F2 -142 47 Hz
PPMCM 0 48645 ppm/cm
HZCM 145 99826 Hz/cm
SD78 - SD76
ASIC NO. 4704
CDCL3+DMSO
ppm
Integral
0.00
2.04
2.30
3.29
3.30
3.35
3.36
3.82
3.83
3.88
3.92
3.94
3.98
5.72
5.73
5.76
5.77
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7.35
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7.67
7.68
1.0000
1.0006
0.0922
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0.4758
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0.0775
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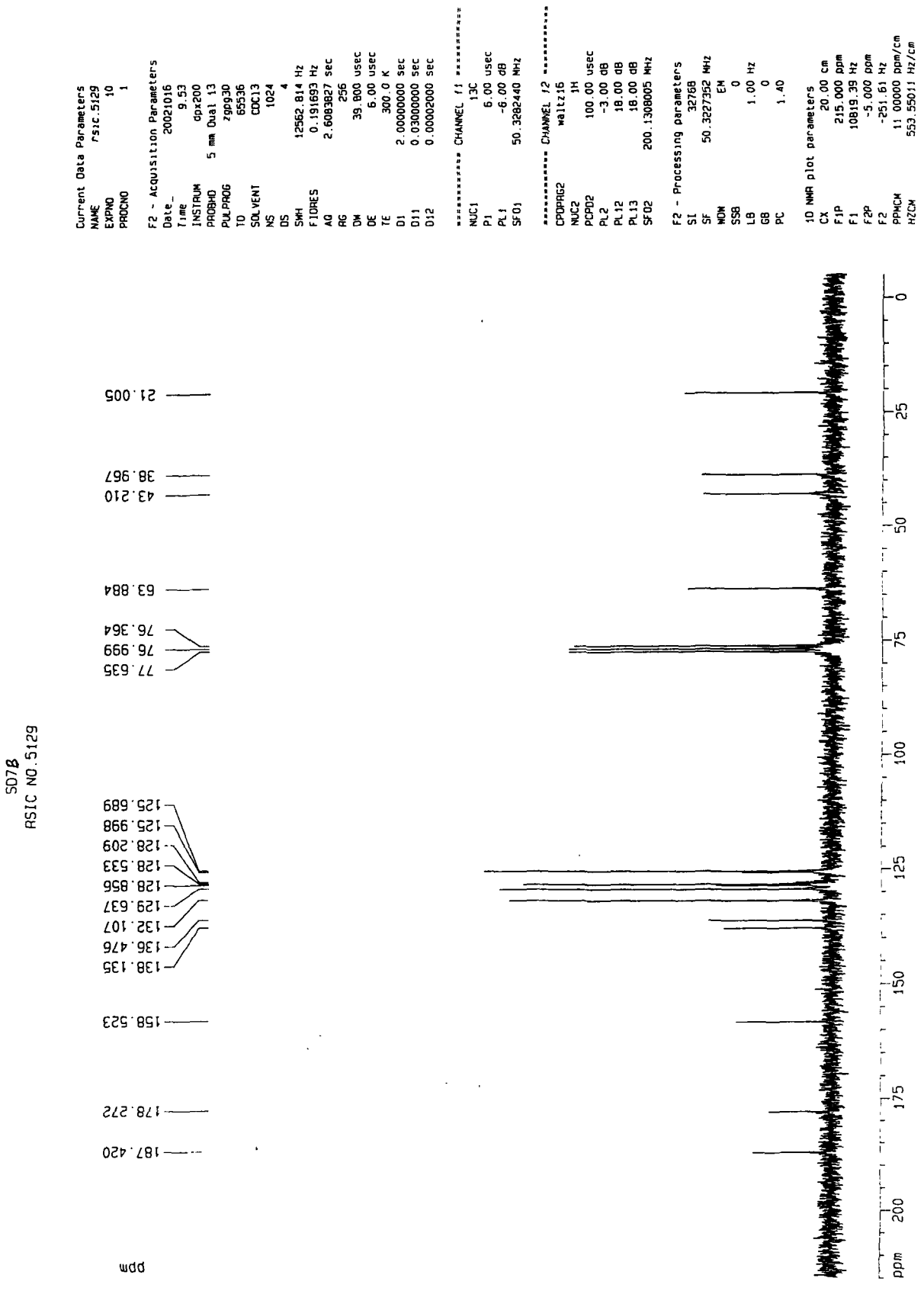
0.0615
0.0872

FIG. 53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PROCNO 1
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DE 6.00 usec
TE 300.0 K
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D11 0.03000000 sec
D12 0.00002000 sec
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NUC1 13C
P1 6.00 usec
PL1 -6.00 dB
SFO1 50.3282440 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
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PL13 18.00 dB
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SSB 0
LB 1.00 Hz
GB 0
PC 1.40
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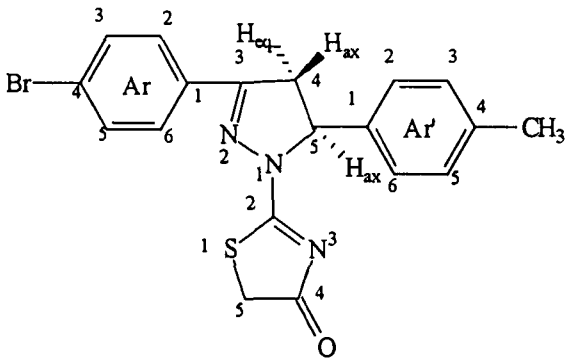
F1P 215.000 ppm
F1 10819.39 Hz
F2P -5.000 ppm
F2 -251.61 Hz
PPMCM 11.00000 ppm/cm
HZCM 553.55011 Hz/cm
21.005
38.967
43.210
63.884
76.364
76.999
77.635
125.689
125.998
128.209
128.533
128.856
129.637
132.107
136.476
138.135
158.523
178.272
187.420
ppm
200
175
150
125
100
75
50
25
0

FIG. 54

TABLE -18 : ^{1}H-NMR and ^{13}C-NMR spectral data of SD_{7B} (24)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)	C-nr	δ (ppm)
4eq	3.35	1H	dd	$J_{4eq,4ax}$=18.0, $J_{4eq,5ax}$=3.90	3	158.52
4ax	3.94	1H	dd	$J_{4eq,4ax}$=18.0, $J_{4ax,5ax}$=11.10	4	43.21
5ax	5.76	1H	dd	$J_{4eq,5ax}$=3.90, $J_{4ax,5ax}$=11.10	5	63.88
5'	3.83	2H	s	–	2'	178.27
Ar-CH_3	2.30	3H	s	–	4'	187.42
2 x Ar	7.11-7.68	8H	br m	–	5'	38.96
					Ar-CH_3	21.00
					2 x Ar	125.69-138.14

Based on the above facts, SD_{7B} was characterized as *2-[3-(4-bromophenyl)-5-(4-methylphenyl)-2-pyrazolin-1-yl]thiazolin-4-one (23)*.



SD_{7B} (24)

Experimental

EXPERIMENTAL

1,3-Bis(2-thienyl)-2-propen-1-one (17)

It was prepared following a published procedure[47] by condensing thiophene-2-aldehyde with 2-acetyl thiophene (prepared from thiophene according to reported procedure[47]) in equimolar ratio, in the presence of 2.5 equivalents of sodium hydroxide. A mixture of thiophene-2-aldehyde (500 mg, 4.46 mmol) and 2-acetyl thiophene (562 mg, 4.46 mmol) in (20 ml) ethanol was kept on an ice bath and to this was added sodium hydroxide (446 mg, 11.15 mmol) dropwise with stirring. It was further stirred 4 h and then worked up as usual. The yellow solid thus obtained was crystallized (acetone-benzene) to yield **(17)** as light yellow crystalline needles, 765 mg (78%), m.p. 89°C, R_f 0.63 (pet. ether - ethyl acetate, 8:2 v/v).

Spectral data of (17)

^{1}H-NMR (acetone-d_6, 400 MHz) : δ_H 7.48 (1H, d, J=15.51 Hz, H-2), 7.94 (1H, d, J=15.51 Hz, H-3), 7.67 (1H, dd, J=3.66 Hz, J=1.07 Hz, Ar'-3), 7.60 (1H, dd, J=3.66, J=1.07 Hz, Ar-3), 7.27 (1H, dd, J=5.04hz, J=3.66 Hz, Ar'-4), 7.18 (1H, dd, J=5.04 Hz, J=3.66 Hz, H-Ar-4), 8.11 (1H, dd, J=5.04 Hz, J=1.07 Hz, Ar'-5), 7.92 (1H, dd, J = 5.03 Hz, J=1.07Hz, Ar-5).

^{13}C-NMR (acetone-d_6, 100 MH$_3$) : δ_C 181.80 (C-1), 121.36 (C-2), 133.06 (C-3), 129-60-146.68 (C-Ar + Ar').

DCI-MS (NH_3) : m/z 221/222/223 [(M+1)/(M+2)/(M+3), 100.0/20.4/11.8], 220 (14.0), 191 (3.7), 137 (3.8), 111 (7.2).

2-[3,5-Bis(2-thienyl)-2-pyrazolin-1-yl]thiocarboxamide SD_{1A} (19) along with thiosemicarbazone, N^1-[1,3-bis(2-thienyl)-2-propen-1-ylidene)thiosemicarbazide SD_1(18)

A mixture of 1,3-bis(2-thienyl)-2-propen-1-one (**17**) (700 mg, 3.18 mmol) and thiosemicarbazide (868 mg, 9.54 mmol) in absolute alcohol (25 ml) was refluxed for 10 h with stirring. The progress of the reaction was monitored by TLC at every 30 minute. After completion, the reaction mixture was concentrated under reduced pressure, extracted with diethyl ether and washed with water until the solution was neutral. The ethereal solution was then kept over Na_2SO_4 overnight, then solvent evaporated and orange-coloured oily residue left was examined by TLC (silica gel 'G' benzene-ethyl acetate, 8:2 v/v). It was found to be a mixture of two components, one minor (upper) and the other major (lower), labelled as SD_1 and SD_{1A}. The oily residue was chromatographed over a silica gel column using benzene-ethyl acetate, (8:2 v/v) as an eluent. Elution of the column first furnished a light yellow coloured solid which on crystallization from benzene-acetone yielded SD_1**(18)** as an orange crystalline needles, 221 mg (15%), m.p. 130 °C, R_f 0.76 (benzene-ethyl acetate, 8:2 v/v).

Spectral data of SD_1(18)

IR (KBr pellet) : υ_{max} cm^{-1} 3420, 3240 (NH), 2915 (CH), 1590 (C=N), 1495 (phenyl), 1180 (C=S), 1070(C-N), 950, 816, 715 cm^{-1}.

^{1}H-NMR (acetone-d_6, 400 MHz) : δ_H 7.21 (1H, d, J=16.02 Hz, H-2), 7.44 (1H, d, J = 16.02 Hz, H-3), 7.53, 7.63 (2H, s, NH_2), 9.98 (1H, s, NH), 7.11-7.60 (6H, br m, H-Ar + Ar').

^{13}C-NMR (acetone-d_6, 100 MHz) : δ_C 116.99 (C-2), 134.34 (C-3), 143.69 (C-1), 180.90 (C=S), 127.60-143.91 (C-Ar + Ar').

DCI-MS (NH_3) : m/z 296/295/294 (15.4/21.2/100.0), 280/279/278/277 (3.1/18.0/4.3/20.8), 260 (3.1), 235 (3.9), 233 (9.6), 218 (2.0), 185/184/183 (3.1/4.3/32.4), 112 (3.9), 77 (8.7).

Further elution of the column yielded a yellow coloured solid which on recrystallization from benzene-acetone afforded **SD_{1A}(19)** as brown crystalline needles, 960 mg (65%), m.p. 138 °C, R_f 0.62 (benzene-ethyl acetate, 8:2 v/v).

Spectral data of SD_{1A} (19)

IR (KBr pellet) : υ_{max} cm^{-1} 3436, 3274 (NH), 2945 (CH), 1576 (C=N), 1463 (phenyl), 1339, 1171 (C=S), 1079 (C-N), 906, 818, 721, 609 cm^{-1}.

^{1}N-NMR (acetone-d_6, 400 MHz) : δ_H 3.42 (1H, dd, J=17.55 Hz, J=2.75 Hz, H-4eq), 4.00 (1H, dd, J=17.55 Hz, J=10.84 Hz, H-4ax), 6.37 (1H, dd, J=2.75, J=10.84, H-5ax), 7.12, 7.40 (2H, s, NH_2), 7.05 (1H, ddd, J=3.66 Hz, J=1.22 Hz, J=0.77 Hz, H-Ar-3), 6.94 (1H, dd, J=3.66 Hz, J=5.04 Hz, H-Ar-4), 7.30 (1H, dd, J=5.04 Hz, J=1.22 Hz, H-Ar-5), 7.55 (1H, dd, J=3.66 Hz, J=1.07 Hz, H-Ar'-3), 7.17 (1H, dd, J=3.66 Hz, J=5.04 Hz, H-Ar'-4), 7.69 (1H, dd, J=5.04 Hz, J=1.07 Hz, H-Ar'-5).

^{13}C-NMR (acetone-d_6, 100 MHz) : δ_C 135.25 (C-3), 43.90 (C-4), 60.12 (C-5), 178.12 (C=S), 152.28 (Ar-2), 131.42 (Ar-3), 128.87 (Ar-4), 125.57 (Ar-5), 146.05 (Ar'-2), 130.62 (Ar'-3), 127.28 (Ar'-4), 125.19 (Ar'-5).

DCI-MS (NH_3) : m/z 296/295/294/293 (15.5/18.5/100.0/6.8), 260(6.0), 237/236/235/234/233 (9.4/15.9/92.1/27.9/7.4), 218 (5.4), 183 (7.1), 171 (4.1), 169 (12.9), 151 (5.3), 109 (4.6), 97 (7.6).

2-[3,5-Bis(2-thienyl)-2-pyrazolin-1-yl]thiazolin-4-one SD_{1B} (20)

A mixture of the pyrazolinyl thiocarboxamide SD_{1A} **(19)** (850 mg, 2.90 mmol), chloroacetic acid (341 mg, 3.63 mmol) and sodium acetate (357 mg, 4.35 mmol) in freshly distilled acetic acid (25 ml) was refluxed with stirring on an oil bath at 120 °C for 35 h. After the reaction was over, the reaction mixture was concentrated under reduced pressure, extracted with diethyl ether and washed with water until the solution became neutral. The ethereal solution was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The yellow-coloured oily residue left was finally examined by TLC (silica gel 'G' benzene-ethyl acetate 8:2 v/v) which showed only one component, labelled as SD_{1B}. The oily residue was chromatographed on a silica gel column using benzene-ethyl acetate (8:2 v/v) as an eluent. Elution of the column furnished a yellow-coloured solid which on crystallization from benzene-acetone (9:1 v/v) afforded SD_{1B} **(20)** as dark brown crystalline needles, 573 mg (56%) m.p. 280 °C, R_f 0.58 (benzene-ethyl acetate, 8:2 v/v).

Spectral data of SD_{1B} (20)

IR (KBr pellet) : υ_{max} cm^{-1} 2818 (CH), 1680 (C=O), 1593 (C=N), 1550 (phenyl), 1470 ($S\text{-}CH_2$), 1385, 1351, 1291, 1224, 1101, 829, 714.

^{1}H-NMR (acetone-d_6, 400 MHz) : δ_H 3.67 (1H, dd, J = 17.85 Hz, J=3.51 Hz, H-4eq), 4.23 (1H, dd, J=17.85 Hz, J=10.84, H-4ax), 6.16 (1H, dd, J=3.51 Hz, J=10.84 Hz, H-5ax), 3.85 (2H, s, H-5'), 7.17 (1H, ddd, J = 3.66 Hz, J=1.22 Hz, J=0.77 Hz, H-Ar-3), 6.99 (1H, dd, J=3.66 Hz, J=5.04 Hz, H-Ar-4), 7.39 (1H, dd, J=1.22 Hz, 5.04 Hz, H-Ar-5), 7.65 (1H, dd, J=3.66 Hz, J=1.22 Hz, H-Ar'-3), 7.24 (1H, dd, J=3.66 Hz, J=5.04 Hz, H-Ar'-4), 7.79 (1H, dd, J=5.04 Hz, J=1.22 Hz, H-Ar'-5).

^{13}C-NMR (acetate-d_6, 100 MHz) : δ_C 156.18 (C-3), 44.54 (C-4), 60.67 (C-5), 178.64 (C-2'), 187.01 (C-4'), 39.30 (C-5'), 126.36-143.38 (C-Ar + Ar').

DCI-MS (NH_3) : m/z 336/335/334/333 (16.1/21.6/100.0/10.2), 236 (4.7), 224 (6.1), 151(2.0), 110 (8.8), 109 (5.3).

1-(4-Bromophenyl)-3-(4-methylphenyl)-2-propen-1-one (21)

It was prepared as described above by condensing 4-methyl benzaldehyde with 4-bromoacetophenone in equimolar ratio in presence of 2.5 equivalent of sodium hydroxide. A mixture of 4-methylbenzaldehyde (700 mg, 5.8 mmol) and 4-bromoacetophenone (1160mg, 5.8 mmol) dissolved in ethanol (25 ml) was kept on an ice bath in 500 ml flask. To this sodium hydroxide (583 mg, 14.6 mmol) was added dropwise with stirring. It was stirred further for 3 h. and then worked up as above. The yellow solid thus obtained was crystallized in ethanol to afforded **(21)** as yellow crystalline needles 1316 mg (75%), m.p. 138 °C, R_f 0.76 (hexane-ethyl acetate, 8:2 v/v).

2-[3-(4-bromophenyl)-5-(4-methylphenyl)-2-pyrazolin-1-yl] thiocarboxamide SD_{7A} (23) along with the adduct thiosemicarbazone, N^1-[3-(4-bromophenyl)-5-(4-methylphenyl)-2-propen-1-ylidene] thiosemicarbazide SD_7 (22)

A mixture of the chalcone **(21)** (1200 mg, 3.98 mmol) and thiosemicarbazide (1088 mg, 11.96 mmol) in absolute alcohol (50 ml) was refluxed with stirring at 80 °C on an oil bath for 10 h. The progress of the reaction was monitored by TLC at every 30 minute. After completion, the reaction mixture was concentrated under reduced pressure, extracted with diethyl ether and washed until the solution was neutral. The ethereal solution was then dried over sodium sulphate, solvent evaporated and the orange-coloured oily residue left was examined by TLC (silica gel 'G', benzene-ethyl

acetate, 8:2 v/v). It was found to be a mixture of two compounds, one minor (upper) and the other major (lower), labelled as **SD_7 (22)** and **SD_{7A} (23).** The oily residue was chromatographed over a silica gel column using benzene-ethyl acetate (8:2 v/v) as an eluent. Elution of the column first furnished a yellow-coloured solid which on crystallization from benzene-acetone afforded **SD_7 (22)** as an orange crystalline needles, 210 mg (14%), m.p. 182 °C, R_f 0.86 (benzene-ethyl acetate).

Spectral data of SD_7 (22)

IR(KBr pellet) : υ_{max} 3464 (NH), 2930 (CH), 1584 (C=N), 1478 (phenyl), 1386, 1326, 1250, 1117, 1072, 981, 867, 805, 768, 712 cm^{-1}.

^{1}H-NMR ($CDCl_3$ + DMSO, 300 MHz) : δ_H 6.36 (1H, d, J=16.20 Hz, H-2, 7.03 (1H, d, J=16.20Hz, H-3), 8.41 (2H, s, NH_2), 10.57 (1H, s, NH), 2.38 (3H, s, H-Ar-CH_3), 7.12-7.75 (8H, br m, H-Ar).

^{13}C-NMR ($CDCl_3$ + DMSO, 75 MHz) : δ_C 148.50(C-1), 115.70(C-2), 135.50 (C-3), 179.0) (C=S), 21.10 (C-Ar-CH_3), 123.50-141.50 (2 x Ar - C).

FAB-Mass (JEOL SX 102/DA-6000) : m/z 374/376 (100.0/93.75), 357/359 (12.50/12.50), 340/342 (14.58/16.66), 315/317 (16.66/16.66), 298/300/ 302 (41.66/45.83/10.42), 235/237(29.16/20.83), 218/220 (14.58/6.24), 200/202/204/206 (2.08/8.33/8.33/4.16), 189/191 (8.33/20.83), 176/178 (4.16/6.24), 165 (20.83), 162 (18.75), 154 (18.75), 136/134 (14.58/4.16), 115/117 (18.75/20.83), 105 (6.24).

Further elution of the column afforded a yellow solid which on crystallization from benzene-acetone yielded **SD_{7A} (23)** as brown crystalline needles, 989 mg (66%), m.p. 200°C, R_f 0.62 (benzene-ethyl acetate, 8:2 v/v).

Spectral data of SD_{7A} (23)

IR (KBr pellet) : 3380 (NH), 2970 (CH), 1590 (C=N), 1535, 1480 (phenyl), 1330, 1115, 1075, 960, 860, 810, 760 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MH_2) : δ_H 3.08 (1H, dd, J=17.10 Hz, J=5.70 Hz, H-4eq), 3.75 (1H, dd, J=17.10Hz, J-12.0 Hz, H-4ax), 5.57 (1H, dd, J=5.70Hz, 12.0 Hz, H-5ax), 7.36(2H, s, NH_2), 2.35 (3H, s, H-Ar-CH_3), 7.09-7.62 (8H, br m, H-Ar).

^{13}C-NMR ($CDCl_3$, 75 MHz) : δ_C 159.90 (C-3), 42.80 (C-4), 61.60 (C-5), 23.7 (C-Ar-CH_3), 123.80-138.80 (2 x Ar- C).

EI-MS : m/z 374/376 (6.06/2.27), 357/359 (9.10/10.60), 340/342 (9.85/ 8.33), 314/316 (63.64/59.10), 299/301 (9.85/6.82), 284/286 (6.06/3.79), 269/271/273 (7.5/9.85/1.52), 235 (7.5), 234 (13.64), 233 (6.82), 226 (3.0), 225 (27.27), 224 (9.09), 223 (29.55), 205/207 (32.58/3.78), 197/199 (20.45/18.18), 189/191 (49.24/100.0), 182/184 (25.76/22.73), 178/180 (12.12/3.03), 169/171 (6.06/6.81), 165/167 (21.21/3.03), 155/157 (9.09/ 10.60), 150/152 (4.54/8.33), 144/146 (17.42/12.12), 128/130 (17.42/4.55), 115/117 (44.70/43.18), 102/104 (43.18/6.82), 91 (47.72), 88/90 (35.60/ 15.15), 77/79 (20.45/7.58), 65 (14.77), 60 (78.03).

2-[3-(4-bromophenyl)-5-(4-methylphenyl)-2-pyrazolin-1-yl]thiazolin-4-one SD_{7B} (24)

A mixture of the pyrazolinyl thiocarboxamide **SD_{7A} (23)** (900 mg, 2.4 mmol), chloroacetic acid (283 mg, 3.0 mmol) and sodium acetate (296 mg, 3.6 mmol) in freshly distilled acetic acid (25 ml) was refluxed with stirring on an oil bath at 120 °C for 35 h. After the reaction was over, the reaction mixture was concentration under reduced pressure, extracted with diethyl ether and washed with water until the solution became neutral. The

ethereal solution was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The yellow-coloured oily residue left was finally examined by TLC (silica gel 'G' benzene-ethyl acetate, 8:2 v/v) which showed only one component, labelled as $\mathbf{SD_{7B}}$. The oily residue was chromatographed on a silica gel column using benzene-ethyl acetate (8:2 v/v) as an eluent. Elution of the column furnished a yellow coloured solid which on crystallization from benzene-acetone (9:1v/v) yielded $\mathbf{SD_{7B}}$ **(24)** as brown crystalline needles, 548 mg (55%), m.p. 230 °C, R_f 0.35 (benzene-ethyl acetate, 8:2 v/v).

Spectral data of SD_{7B} (24)

IR (KBr pellet) : υ_{max} 2964 (CH), 1699 (C=O), 1593 (C=N), 1538 (phenyl), 1486 (S-CH_2), 1389, 1331, 1211, 1111, 1006, 946, 867, 820, 707.

^{1}H-NMR ($CDCl_3$ + DMSO, 300 MHz) : δ_H 3.35 (1H, dd, J=18.0 Hz, J=3.90 Hz, H-4eq), 3.94 (1H, dd, J = 18.0 Hz, J=11.10 Hz, H-4ax), 5.76 (1H, dd, J=3.90, J=11.10 Hz, H-5ax), 3.83 (2H, s, H-5'), 2.30 (3H, s, H-Ar-CH_3), 7.11-7.68 (8H, br m, H-Ar).

^{13}C-NMR ($CDCl_3$, 75 MHz) : δ_C 158.52 (C-3), 43.21 (C-4), 63.88 (C-5), 178.27 (C-2'), 187.42 (C-4'), 38.96 (C-5'), 21.0 (C-Ar-CH_3), 125.69-138.14 (2 x Ar-C).

EIMS : m/z 415/417 (28.78/2.27), 386/388 (3.03/1.52), 380/382 (2.27/ 2.27), 366/368 (1.52/1.66), 338/340/342(1.52/2.27/1.0), 308/310 (9.84/ 6.82), 311/313 (2.0/1.8), 298/300 (6.06/4.55), 284/286 (2.27/1.14), 269/ 271 (2.27/0.90), 258/260 (1.52/1.52), 249/251 (0.75/1.52), 231/232/233 (9.85/89.39/31.82), 217/218/219 (41.66/9.09/3.79), 202/204 (12.12/ 34.85), 195/197 (13.64/9.09), 189/190/191 (12.12/21/21.21), 181/183 (17.42/15.15), 155/157 (15.15/18.18), 152 (2.27), 151 (2.20), 150 (2.65), 149 (8.71), 148 (10.60), 147 (3.03), 146 (1.51), 145 (4.54), 144 (9.85), 143

(6.06), 142 (5.30), 141 (9.09), 140 (7.57), 139 (4.54), 138 (7.57), 137 (6.82), 119 (8.33), 118, (67.42), 117, 100.0), 116 (15.15), 115 (50.76), 106 (5.30), 105 (15.53), 104 (3.78), 103 (16.28), 102 (20.15), 101 (5.30), 92 (7.5), 91 (47.72), 86 (21.21), 79 (2.27), 78 (6.06), 77 (12.88), 76 (17.42), 75 (11.36), 72 (11.06), 68 (7.58), 65 (9.09), 63 (4.55), 52 (5.30), 50 (3.78), 46 (41.66).

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Chapter - 4

1,3,3-Tris(p-chlorophenyl)propene from Chalcone

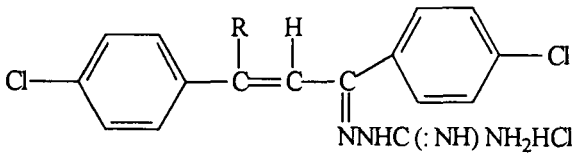
Theoretical

THEORETICAL

New synthetic insecticides are discovered in two ways. The first and most important, atleast until recent years, is discovery by accident, guided of course by past experience. The second is by exploration of groups of compounds related to logical method of synthesizing new insecticides is to combine certain chemical radicals of known value by linkage that may be expected to enhance toxic properties. Organophosphorus esters have played an extremly important part in insect control, and despite modern developments are still used on a wide scale. In contrast to the organochlorine insecticides, they degrade readily in the environment. In organochlorine insecticides of type II 'DDT' (dichlorodiphenyl trichloroethane) and BHC (benzene hexachloride) are most frequently used. DDT has been reported to effective against more than one hundred well-known insect,pests damaging crops and plants grown for man's benifit, e.g. bollworm, codlus moth, colorado potatobeetle etc. DDT is not a cure-all. Some important pests not controlled by DDT include the mexican bee beetle, grass hoppers (various species), cotton leaf-worm, etc. The mode of action, which is now well authenticated and understood, involves the irreversible inhibition of the enzyme acetylcholinesterase, which is essential to nervous conduction in insects, by phosphorylation of a hydroxy group at the active site. Thiophosphoric ester are usually preferred because of their greater stability, but it is important to note that they are only poor inhibitors of the enzyme, and are rapidly oxidized in the insect to much more toxic phosphoric esters. Since acetylcholinesterase is a vital enzyme in vertebrates as well as insects, the mammalian toxicity of many organophosphorus insecticides is high. However, differences in distribution and metabolism in insects and mammals make some esters surprisingly safe.

The widespread usage of the organic insecticides has resulted in the appearance of resistance in mosquitoes, German cockroach, Cabbage worms, Leaf Hoppers, Thrips, Aphids, Mites and Ticks. However, it remained for the widespread development of resistance by the housefly, *Musca domestica* to provided a conclusive demonstration of the importance of the problems of insecticides resistance from agricultural and public health stand points has stimulated a large volume of useful research into the formulation of different insecticides and synthesis of their derivatives. Extensive series of organic compounds were surveyed for their general insecticides value, especially in the period from 1917-1928 by William Moore at the University of Minnesota, by C.H. Richardson, R.C. Roark and R.T. Cotton of the U.S. Department of Agriculture and F. Tafferfield of the Rothamsted Experimental Station in England. By means of such studies many of the chemical structure which would contribute to insecticide effectiveness became more and more evident. However, as Gilman *et al.*[1] said "we are still at the emperical stage, and rather crude emperical stage in many respects, in correlating chemical constitution with physiological action on practically all type of living things". In general, this statement still holds true.

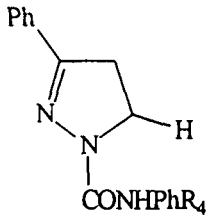
Literature survey revealed that many attempts have been made for the synthesis of new organic insecticides from *4,4'-dichloro chalcone* and using other substrates. Chalcones constitute an important group of natural products and some of them possess a wide range of biological activities such as antitumor[2-3], antibacterial[4-7], antifungal[7-10], anti-inflammatory[11-12], antimicrobial[13-16], anti-cancer[17], prostaglandin binding[18] and insect antifeedant[19]. W.H. David *et al.*[20] synthesized 1,3-bis(4-chlorophenyl)-2-propen-1-one **(I)** gauny hydrazone hydrochloride and analogs as antimalarial.



R = H, Me, *p*-Cl C_6H_4

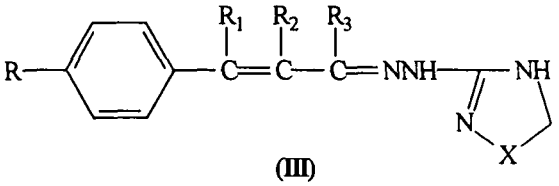
(I)

Mulder *et al.*[21] reported the synthesis of insecticidal 1-(phenyl carbamoyl)-2-pyrazolines **(II)** from substituted chalcones and tested against *Laptinotarsa decemlineata*. Pyrazoline derivatives of the chalcone were also reported as insecticides. A.S. Tomcufcik *et al.*[22] prepared tuberculostatic hydrazones **(III)** by treating chalcones with hydrazines.



(II)

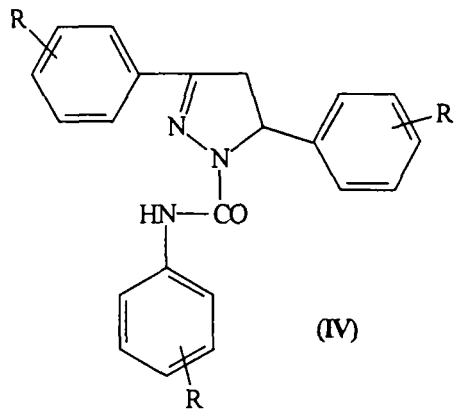
R_4 = 3,4-Cl_2, 4-Cl, 4-iodo etc.



(III)

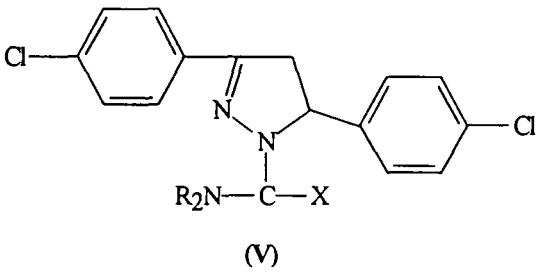
R = Cl, OEt, Ph, CF_3, Br etc.
R_1 = H, 4-Cl C_6H_4, 2-naphthyl etc.
R_2 = H, Me
R_3 = substituted phenyl, 2-naphthyl
X = $(CH_2)_{1-3}$

Some new class of insecticides[23], 1-phenyl carbamoyl-2-pyrazolines **(IV-V)** have been prepared and their insecticidal properties were evaluated on the larval stages of *Aeedes aegypti*, *Pieris brassicae* and *Leptinotarsa decemlineata*. Recently the substituted 2-amino-3,4-dihydropyridine derivatives were synthesized and they are used in drug.



(IV)

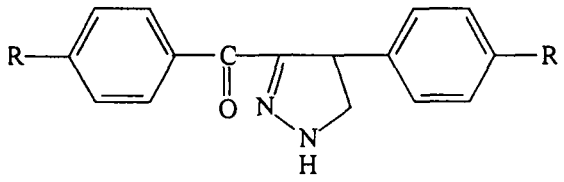
R = H or alkyl or halo



(V)

R_2 = H
X = O

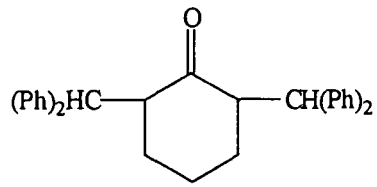
Besides the synthesis of insecticidal compounds many workers synthesized the derivatives of chalcone. Bhasker *et al.*[24] synthesized 3-aroyl-4-aryl-2-pyrazolines (**VI**).



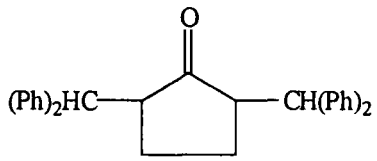
(VI)

R = H or alkyl or halo

V.D. Orlov *et al* [25] carried out the arylation of α,β-unsaturated ketones and prepared a number of chalcones analogue beside the cycloalkanones.

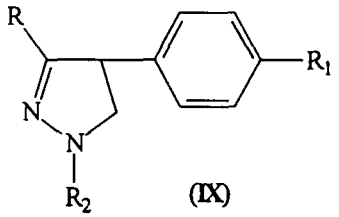


(VII)



(VIII)

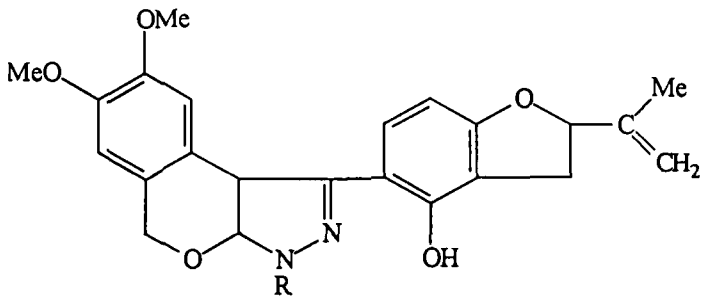
O. Shimizu *et al.*[26] have synthesized insecticidal 1-carbamoyl-4-phenyl pyrazoline derivatives (**IX**).



(IX)

R = alkyl or halo
R_1 = halo or alkyl
R_2 = $CONHR_3$

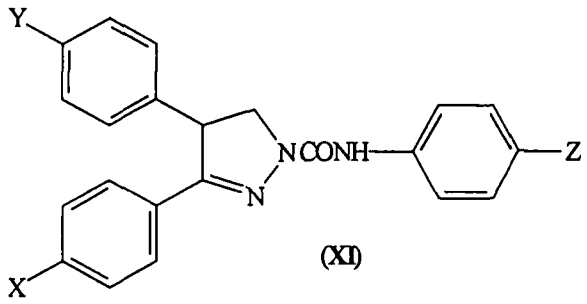
S. Nisaku *et al.*[27] have synthesized benzopyranopyrazolines (**X**). These compounds were potential useful as insecticides and analgesic.



(X)

R = H, Me, CH_2CH_2OH, Ph, tolyl

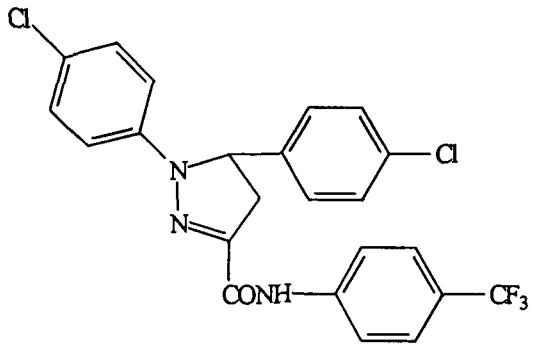
N. Harribert *et al.*[28] have prepared diphenyl-2-pyrazoline-1-carboxamides **(XI)** and were tested as insecticides, acaricides and ectoparasiticides.



(XI)

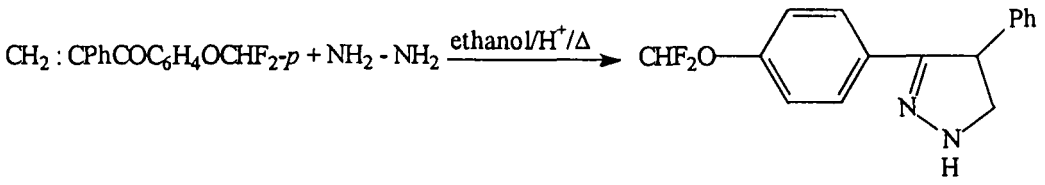
X = H, Cl, F
Y = CHO, Cl.F, F_2
Z = H, C_{1-4} alkyl, CF_3, C_{1-4} (halo)

S. Thomas[29] reported the synthesis of insecticidal pyrazoline carboxamides **(XII)** and tested against *Spodoptera frugiperda larvae*.



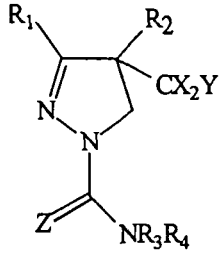
(XII)

O. Kiyomi *et al.*[30] have synthesized insecticidal 3-difluoromethoxy-phenyl-1-phenyl(carbamoyl-2-pyrazoline) **(XIII)**.



(XIII)

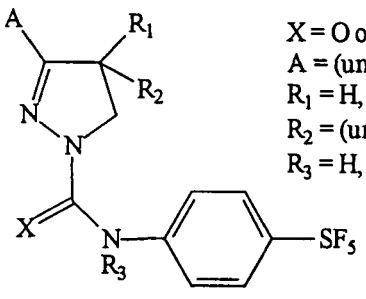
1-carbamoyl-4-halomethyl-4,5-dihydro pyrazoles[31] **(XIV)** have been synthesized and their insecticidal and acaricidal properties were evaluated for *Heliothis virescens*.



R_1 = R 4 = substituted Ph
R_2 = H, alkyl, alkoxy carbonyl etc.
R_3 = H, alkyl, akloxy carbonyl etc.
X = halo
Y = H, halo, halo alkyl
Z = O, S

(XIV)

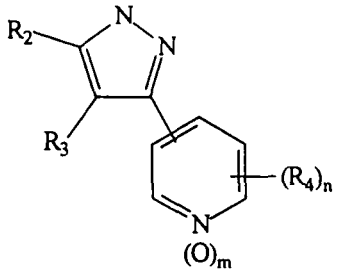
Some new dihydropyrazole **(XV)** compound[32] have been prepared and these were tested as insecticidal, acaricidal. These compounds gave 80-100% kill of *Heliothis verscens, spodoptera exiguo* and *Diabrotica balteata*, 40-79% kill of *Myzus persicae* and <40% kill of *Tetranychus urtica*.



X = O or S
A = (un) substituted aryl
R_1 = H, (un) substituted alkyl or aryl
R_2 = (un) substituted alkyl
R_3 = H, acyl, (un) substituted alkyl

(XV)

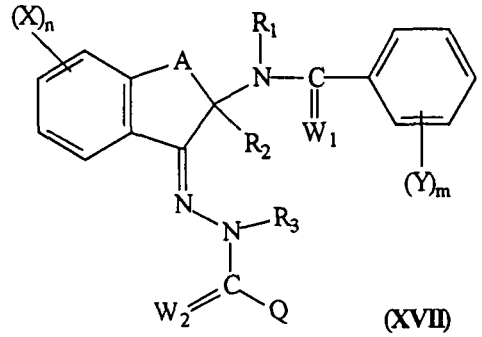
S. Otto *et al.*[33] have prepared pyridylpyrazoles **(XVI)** and these compounds were evaluated as herbicides, insecticides and acaricides.



(XVI)

m = 0, 1
n = 1-3
R_1 = H, (substituted) alkyl, alkenyl, alkynyl
R_2 = H, NO_2, OH, SH, CN, halo etc.
R_3 = H, cyano, halo etc.
R_4 = NO_2, cyano, CO_2H, OH, SH etc.

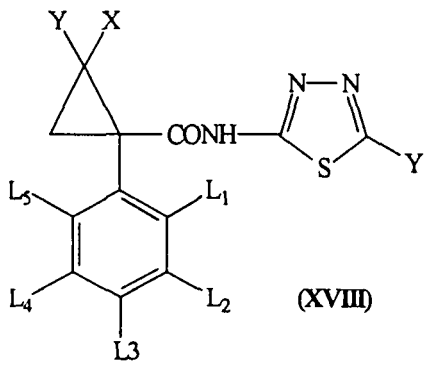
M. Takeshi *et al.*[34] have synthesized hydrazono (tetrahydronaphthalenyl) benzamides **(XVII)** as an insecticides and acaricides. These compounds showed the potential activity against *Spodoptera titura*.



(XVII)

A = CH_2, CH_2CH_3 etc.
Q = H, C_{1-12} alkyl, C_{1-12} haloalkyl etc.
W_1 = W_2 = O, S
X = Y = H, halo, cyano, SCN, SF_5
R_1 = H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cyclo alkyl etc.
R_2 = R_3 = H, C_{1-6} alkyl etc.
m = 1-4
n = 1-5

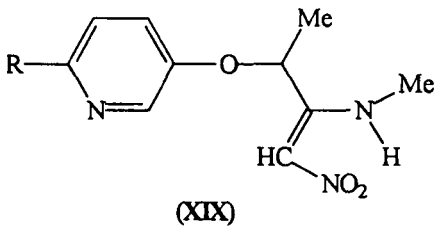
O. Itaru *et al.*[35] have prepared N-thiadiazolyl cyclopropane carboxamides **(XVIII)** and these were evaluated as insecticides, acaricides. These compounds show decreased residual toxicity or cause little or no environmental pollution.



(XVIII)

L_1 - L_5 = H, (halo) alkyl, alkoxy, halo
X = halo, H
Y = halo alkyl

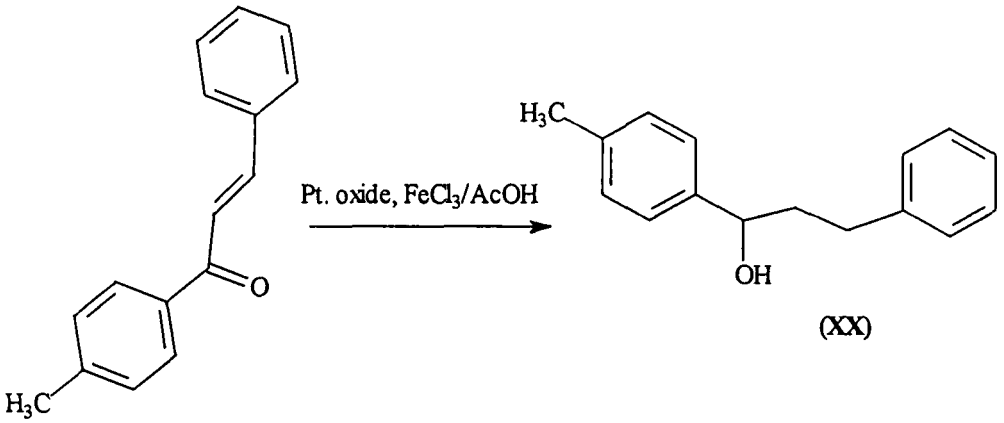
M.L. Dean *et al.*[36] have synthesized a novel heterocyclic nitroalkenes **(XIX)** which were found potential as acaricides and insecticides.



(XIX)

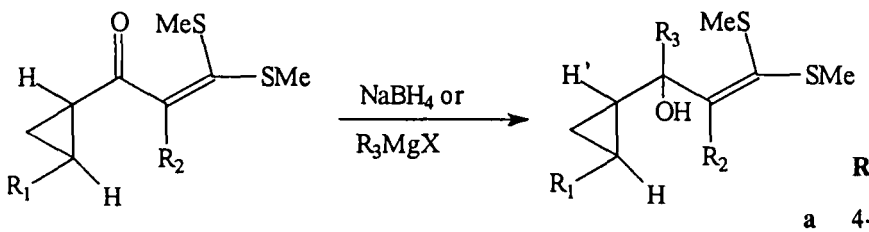
R = halo or alkyl

C. Weygand *et al.*[37] have synthesized 1-(4-methylphenyl)-3-(phenyl)-1-propanol **(XX)** by the reduction of *p*-methyl chalcone with Pt. oxide and ferric chloride in presence of acetic acid.



(XX)

B. Patro *et al.*[38] carried out the sodium borohydride reduction (or Grignard addition) of the cyclopropyl ketones to afford cyclopropyl carbinols **(XXI)**.



(XXI)

	R_1	R_2	R_3
a	4-$MeOC_6H_4$	H	Me
b	C_6H_5	H	Me
c	4-$MeOC_6H_4$	Me	Me

Discussion

DISCUSSION

SUMMARY

The work described in this chapter consists of the preparation of -

(i) 1,3,3-tris(4-chlorophenyl)propan-1-ol **Q** *(25) from 1,3,3-tris(4-chlorophenyl)propan-1-one* **P** *(2) obtained by the addition of chlorobenzene to 4,4'-dichlorochalcone (1).*

(ii) 1,3,3-tris (4-chlorophenyl)prop-1-ene **R** *(26) by the dehydration of* **Q** *(25) in the presence of p-toluenesulphonic acid in dry benzene.*

Structures are established on the basis of IR, Mass, ^{1}H-NMR and ^{13}C-NMR spectral studies The compound (25) has been evaluated for anticancer activity.

INTRODUCTION

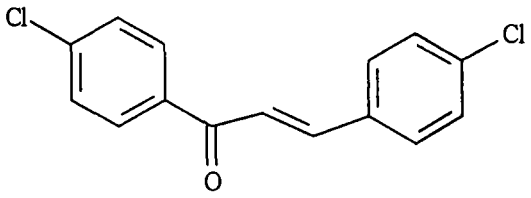
The toxicity of hydrocarbons is in general increased when the following elements or radicals are introduced into the molecule, Cl, Br, I, OH, SH, SO_2, NO_2 and NH_2. Organochlorine compounds are reported to be potent insecticidal[21,23,29], antitumor[2-3], antimalarial[20] and acaricidal[31-32] Keeping in view of the importance of organochlorine compounds, effort has been made for search of some new or improved organochlorine compounds as derivatives of chalcones, and we have prepared the following organochlorine compounds :

(i) 1,3,3-tris(4-chlorophenyl)-propan-1-ol **Q** *(25) from 1,3,3-tris(4-chlorophenyl)propan-1-one* **P** *(2) obtained by the addition of chlorobenzene to 4,4'-dichlorochalcone (1).*

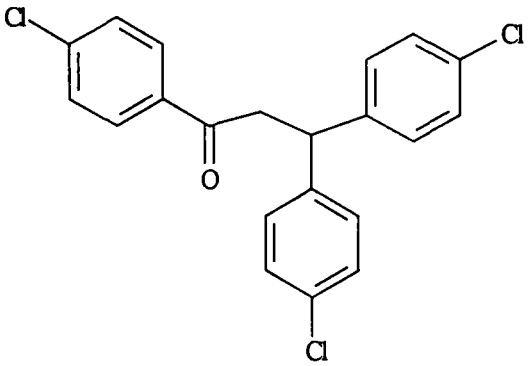
(ii) 1,3,3-tris(4-chlorophenyl)prop-1-ene **R** *(26) from* **Q** *(25) by dehydration in the presence of p-toluenesulphonic acid in dry benzene.*

Structural assignments, stereochemistry and biological assay are discussed. Screening results of compound **Q** (25) are summarized for

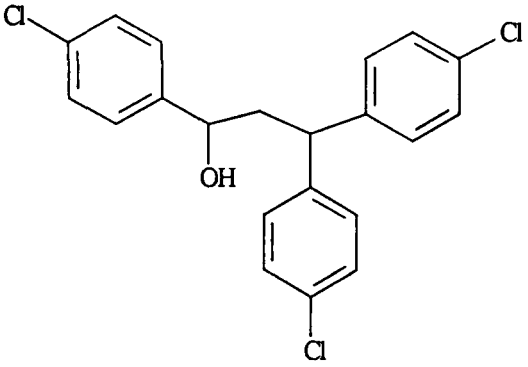
anticancer activity against 3-cell lines of three types of human cancers : lung, breast and CNS and then against 60-cell lines of nine types of human cancers: leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast **(DETAILS IN CHAPTER-6)**.



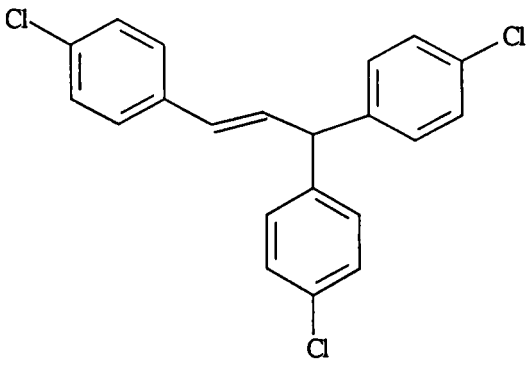
(1)



P (2)



Q (25)



R (26)

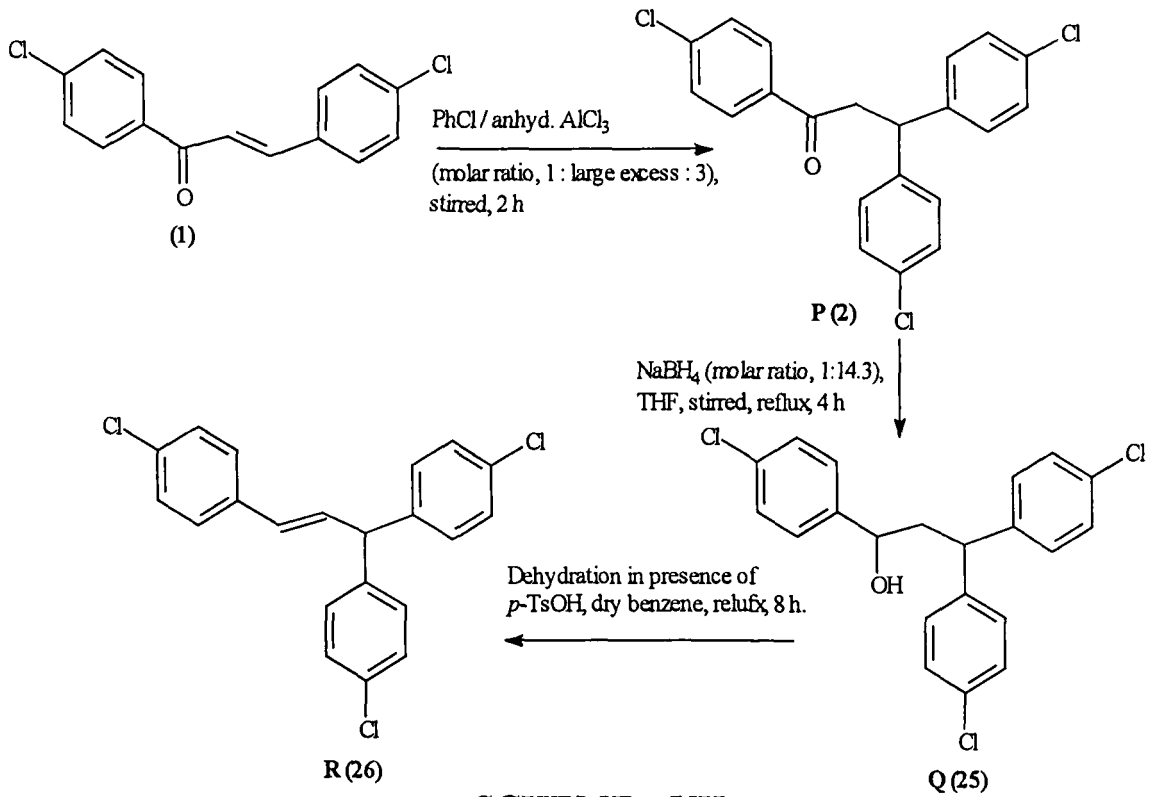
RESULTS AND DISCUSSION

The synthesis of target compound **R (26)** was performed in three steps :

Step 1 : The adduct **P (2)** was prepared from chalcone **(1)** using chlorobenzene in presence of anhydrous $AlCl_3$ exactly as described in **CHAPTER-1.**

Step 2 : The carbonyl group of the 1,3,3-tris(4-chlorophenyl)propan-1-one **P (2)** was reduced with sodium borohydride (molar ratio, 1:14.31) in THF with stirring for 18 h and the products purified by column chromatography over silica gel using pet. ether-benzene as eluent which afforded **Q (25)** in 90.71% yield.

Step 3 : The dehydration of 1,3,3-tris(4-chlorophenyl)propan-1-ol **Q (25)** was carried out by refluxing it in dry benzene in the presence of *p*-toluenesulphonic acid for 4 h with azeotropic removal of water. The product was crystallized from benzene-acetone (8:2 v/v) to yield the final product **R (26)** in 85% yield **(SCHEME-VII).**



SCHEME - VII

Preparation of 1,3,3-tris(4-chlorophenyl)propan-1-one P (2) from 4,4'-dichlorochalone (1) using excess of chlorobenzene in the presence of anhydrous aluminium chloride

The preparation and structure of compound (2) were discussed in CHAPTER-1.

Reduction of P (2) with sodium borohydride (Preparation of 1,3,3-tris(4-chlorophenyl)propan-1-ol Q (25) from 1,3,3-tris(4-chlorophenyl)propan-1-one P (2) by reduction with sodium borohydride in THF)

The compound (25) was then prepared by refluxing a solution of sodium borohydride and 1,3,3-tris(4-chlorophenyl)propan-1-one (2) (molar ratio, 1:14.31) in tetrahydrofuran with stirring for 14 h. The tetrahydrofuran solvents was distilled off under reduced pressure and the residue extracted with ethyl acetate, washed with water to remove unreacted sodium borohydride and dried over sodium sulphate. On evaporation of solvent, an oily residue was obtained. The products on purification by column chromatography (silica gel, pet. ether-benzene, 8:2 v/v) afforded **Q (25)** as white semisolid mass in 90.71% yield.

Structure Elucidation of Q (25)

It is a white semisolid mass and appears brown on exposure to iodine vapours (TLC). The constitution of **Q** has been established by FT-IR, DCI-MS, ^{1}H-NMR, and ^{13}C-NMR spectra. The IR spectrum (KBr) displayed characteristic absorption bands at 3580 (-OH), 2939, 2923 (C-H), 1597, 1576 (phenyl), 1517, 1490, 1404, 1344, 1293, 1180, 1091, 1013, 960, 898, 832, 771, 754, 735, 722, 676, 568, 528 cm^{-1}. The DCI-MS (NH_3 as reagent gas) spectrum (**FIG. 55**) of **Q (25)** showed a set of [M^+] peaks at m/z 390/392/394 (17.07/14.63/2.44), confirming its molecular weights 390/392/394 which is consistent with molecular formula [$C_{21}H_{17}Cl_3O$]. The sets of peaks

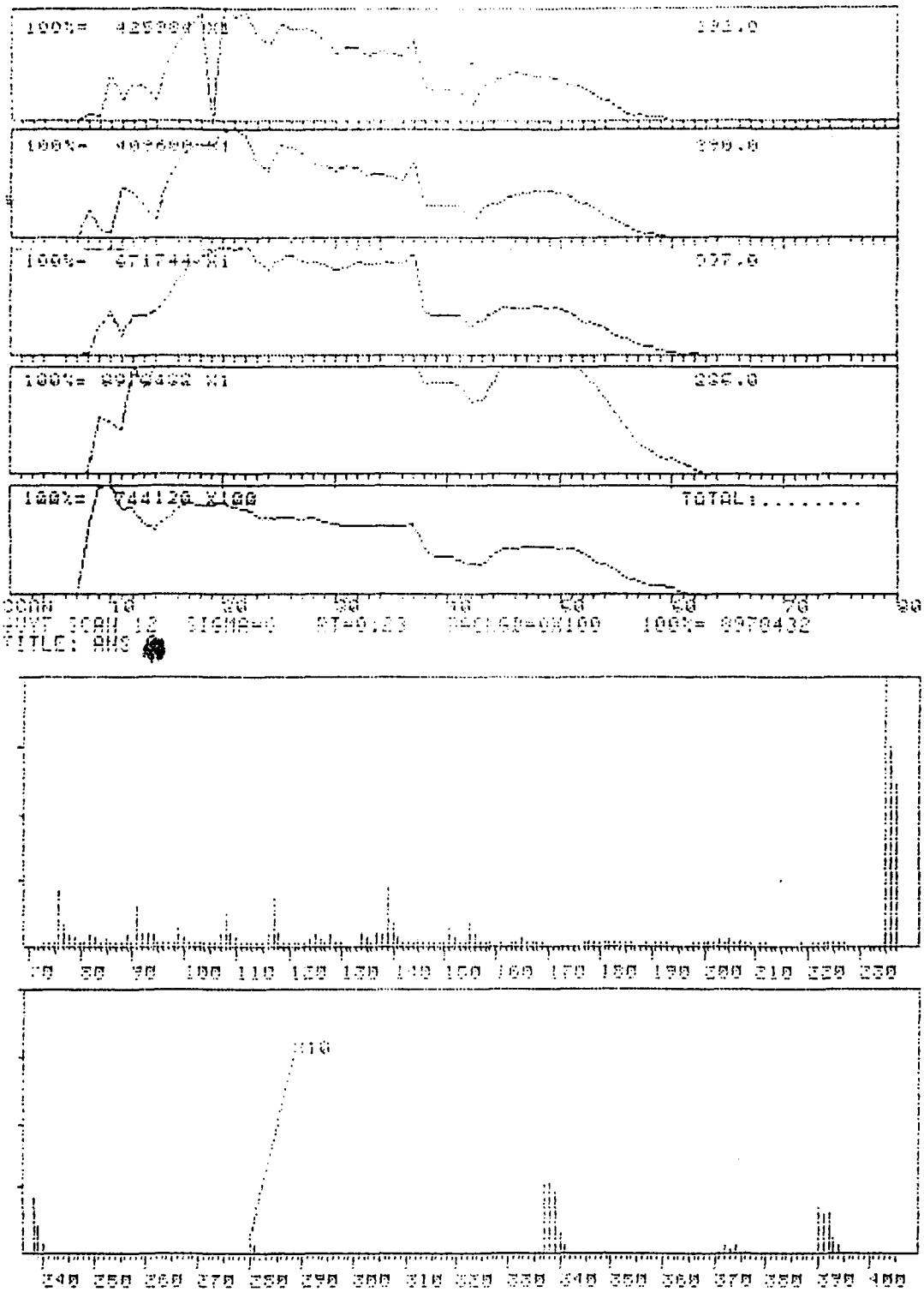


FIG. 55

.	76.00	20.7	.	99.00	7.0	.	128.00	4.8	.	155.00	0.5
.	77.00	8.1	.	107.00	4.8	.	134.00	5.6	.	235.00	100.0
.	82.00	5.1	.	108.00	13.6	.	137.00	5.9	.	236.00	74.8
.	91.00	15.6	.	109.00	5.4	.	138.00	4.6	.	237.00	60.5
.	92.00	5.7	.	117.00	19.0	.	139.00	22.5	.	238.00	21.7
.	93.00	6.2	.	118.00	6.2	.	140.00	8.3	.	239.00	11.3
.	94.00	4.7	.	125.00	5.2	.	151.00	8.5	.	240.00	4.9

at m/z 155/157 (8.5/2.40) $[M-(p\text{-}ClC_6H_4)_2CH]^+$ and at m/z 235/237/239 (100.0/60.5/11.3) $[M-C_8H_8ClO]^+$ were arised by the cleavage of 2-3 bond as shown in **CHART-18**.

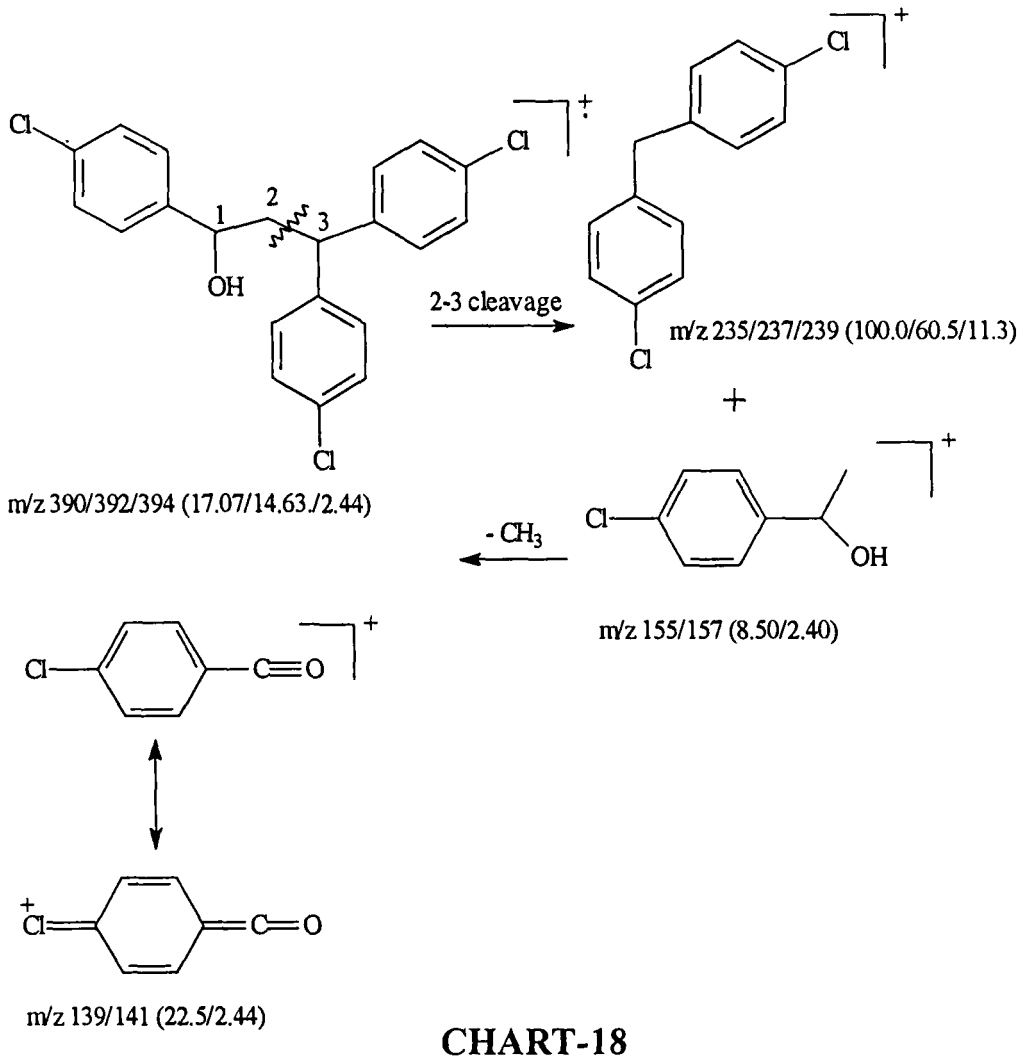


CHART-18

The ^{1}H-NMR (**FIG. 56**) and ^{13}C-NMR (**FIG. 57**) spectra of **Q** dissolved in acetone-d_6 showed signals as assigned (**TABLE-19**). The assignments of all ^{1}H-NMR and ^{13}C-NMR signals to individual H- and C-atoms have been performed on the basis of typical chemical shift values, multiplicity and relative integrations. The ^{1}H-NMR spectrum of **Q** showed three triple

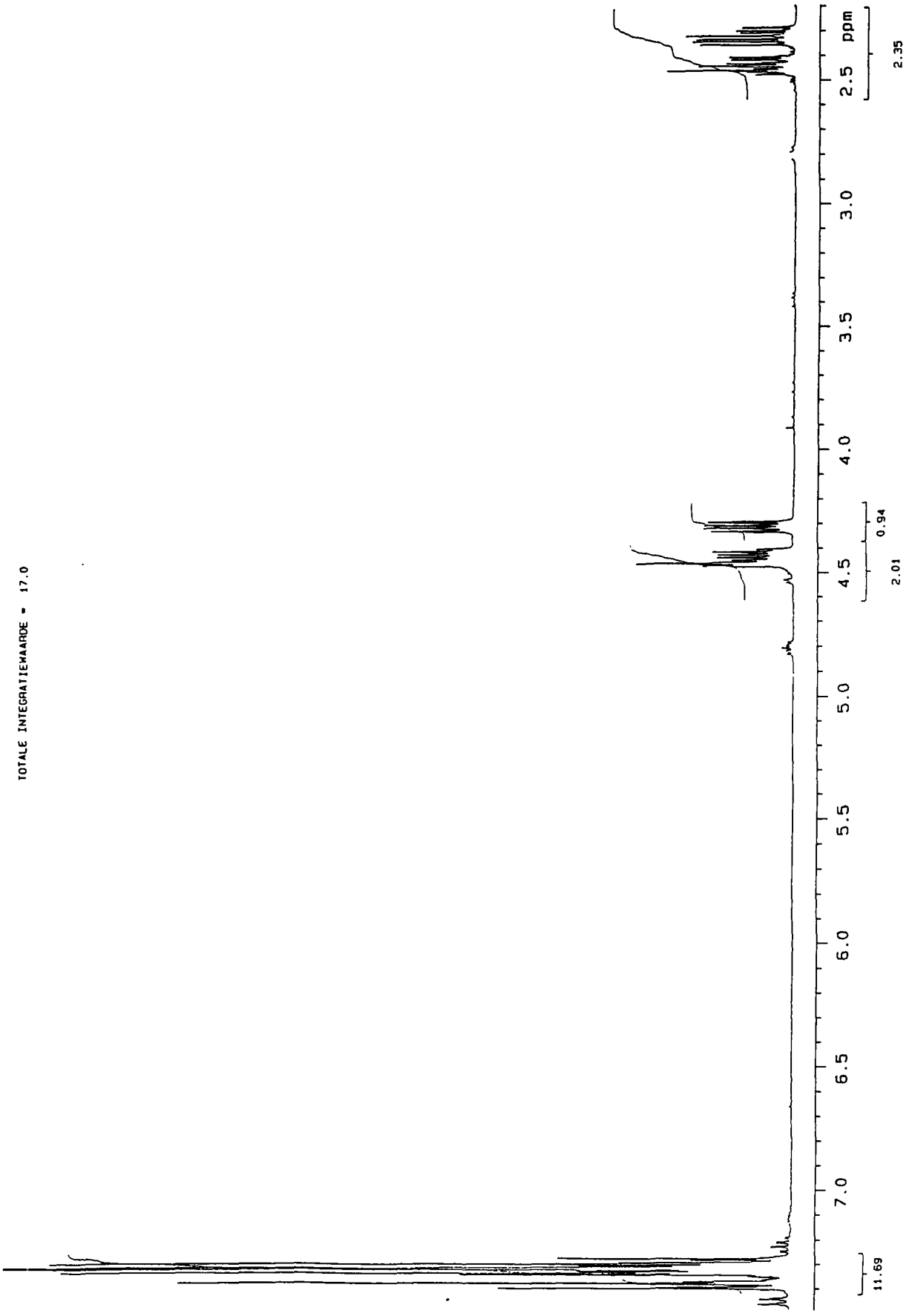

TOTALE INTEGRATIEWAARDE = 17.0
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5 ppm
11.69
2.01
0.94
2.35

FIG. 56

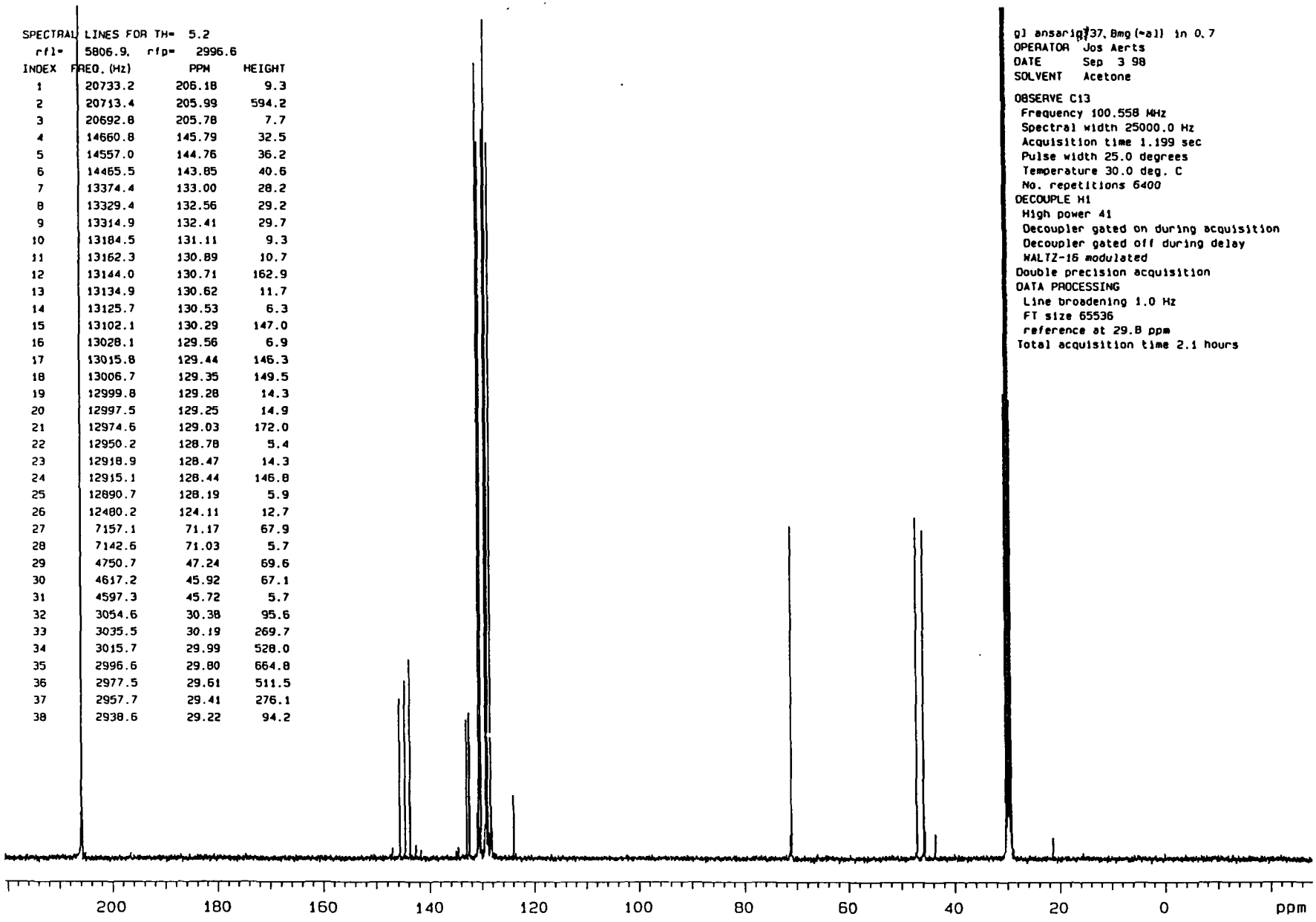

SPECTRAL LINES FOR TH= 5.2
rfl= 5806.9, rfp= 2996.6
INDEX FREQ.(Hz) PPM HEIGHT
1 20733.2 206.18 9.3
2 20713.4 205.99 594.2
3 20692.8 205.78 7.7
4 14660.8 145.79 32.5
5 14557.0 144.76 36.2
6 14465.5 143.85 40.6
7 13374.4 133.00 28.2
8 13329.4 132.56 29.2
9 13314.9 132.41 29.7
10 13184.5 131.11 9.3
11 13162.3 130.89 10.7
12 13144.0 130.71 162.9
13 13134.9 130.62 11.7
14 13125.7 130.53 6.3
15 13102.1 130.29 147.0
16 13028.1 129.56 6.9
17 13015.8 129.44 146.3
18 13006.7 129.35 149.5
19 12999.8 129.28 14.3
20 12997.5 129.25 14.9
21 12974.6 129.03 172.0
22 12950.2 128.78 5.4
23 12918.9 128.47 14.3
24 12915.1 128.44 146.8
25 12890.7 128.19 5.9
26 12480.2 124.11 12.7
27 7157.1 71.17 67.9
28 7142.6 71.03 5.7
29 4750.7 47.24 69.6
30 4617.2 45.92 67.1
31 4597.3 45.72 5.7
32 3054.6 30.38 95.6
33 3035.5 30.19 269.7
34 3015.7 29.99 528.0
35 2996.6 29.80 664.8
36 2977.5 29.61 511.5
37 2957.7 29.41 276.1
38 2938.6 29.22 94.2
g] ansarig]37.8mg(=al) in 0.7
OPERATOR Jos Aerts
DATE Sep 3 98
SOLVENT Acetone
OBSERVE C13
Frequency 100.558 MHz
Spectral width 25000.0 Hz
Acquisition time 1.199 sec
Pulse width 25.0 degrees
Temperature 30.0 deg. C
No. repetitions 6400
DECOUPLE H1
High power 41
Decoupler gated on during acquisition
Decoupler gated off during delay
WALTZ-16 modulated
Double precision acquisition
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
reference at 29.8 ppm
Total acquisition time 2.1 hours
200
180
160
140
120
100
80
60
40
20
0
ppm

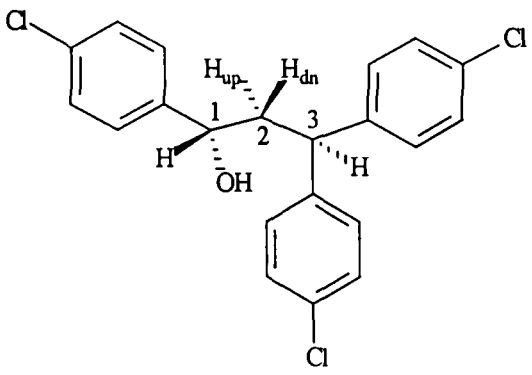
FIG. 57

TABLE -19 : ^{1}H-NMR and ^{13}C-NMR spectral data of Q (25)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)	C-nr	δ (ppm)
OH	4.47	1H	d	$J_{1,OH}$ = 4.28	1	71.17
1	4.42	1H	ddd	$J_{2up,1}$ = 8.85, $J_{2dn,1}$ = 9.01	2	45.92
				$J_{1,OH}$ = 4.28		
2up	2.32	1H	ddd	$J_{2up,2dn}$=14.04, $J_{2up,3}$=5.65	3	47.24
				$J_{2up,1}$ = 8.85		
2dn	2.46	1H	ddd	$J_{2up,2dn}$ = 14.04, $J_{2dn,3}$=10.07	3 x Ar	124.11-145.79
				$J_{2dn,1}$ = 9.01		
3	4.32	1H	dd	$J_{2up,3}$=5.65, $J_{2dn,3}$=10.07		
3 x Ar	7.20-7.50	12H	brm	–		

doublets due to geminal and vicinal coupling of the two diastereotopic protons at C-2 and the two methine adjacent protons at C-1, C-3 positions. The two triple double doublets appeared at δ2.32 and δ2.46 with coupling constants J=14.04 Hz, J=5.65Hz, J=8.85 Hz and J=14.04 Hz, J=10.07 Hz, J = 9.01 Hz to H-2up and H-2dn respectively. Especially according to carplus[39], the coupling constant $J_{2up,3}$ and $J_{2dn,3}$ indicate a synclinal position of H-3 relative to the diastereotopic hydrogen atoms H-2up and H-2dn. The third triple doublet at δ4.42 with coupling constants J=8.85 Hz, J=9.01 Hz, J=4.28 Hz due to vicinal coupling with two magnetically non equivalent protons of methylene group at C-2 position. A double doublet at δ4.32 with coupling constants J=5.65 Hz and J=10.07 was assigned to methine proton at C-3. A doublet at δ4.47 with coupling constant J=4.28 Hz was assigned to alcoholic group proton at C-1. The signals for aromatic protons appeared as A_2B_2 pattern and were assigned for three aromatic rings as shown in **TABLE-19**. The ^{13}C-NMR spectrum of **Q (TABLE-19)** showed signals which are in strong agreement with the assigned structure. The carbon signals at δ71.17 and δ45.92 were attributed to C-1 and C-2 carbons. An another signal at δ47.24 was assigned to C-3 carbon. The signals for aromatic carbons were observed at δ124.11-145.79.

Based on the above spectral evidence, **Q** was characterized as *1,3,3-tris(4-chlorophenyl)propan-1-ol* ***(25)***.



Q (25)

Preparation of 1,3,3-tris(4-chlorophenyl)prop-1-ene R (26) from 1,3,3-tris(4-chlorophenyl)propan-1-ol Q (25) by dehydration in the presence of *p*-toluenesulphonic acid in dry benzene

1,3,3-tris(4-chlorophenyl)propan-1-ol **Q (25)** was dissolved in dry benzene and allowed to reflux with stirring on an oil bath at 80 °C for 4 h in presence of a catalytic amount of *p*-TsOH. TLC examination (silica gel, benzene-diethyl ether, 9:1 v/v) showed almost complete conversion of **Q** to a new compound labelled as **R**. The reaction mixture was concentrated, extracted with diethyl ether, washed with water to remove the acid and dried over sodium sulphate. On evaporation of the solvent, a white residue was obtained, which on recrystallization with benzene-acetone afforded white crystalline globules of **R (26)** in 85% yield.

Structure Elucidation of R (26)

It is a white crystalline globules, m.p. 220 °C and appears light brown colour on exposure to iodine vapours (TLC). The constitution of **R** has been established by FAB-MS, ^{1}H-NMR, ^{13}C-NMR spectra and also by comparison with the spectra of **Q (25)**. The FAB-MS spectrum **(FIG. 58)** showed a set of peaks at m/z 373/375/377/379 (27.08/9.75/1.0/0.8) corresponding with $[M+1]^+$ $[C_{21}H_{15}Cl_3]$, which confirmed its molecular weight (372). This molecular weight corresponds with the molecular weight of **Q (25)** (390) minus one molecule of water. The set of peaks at m/z 337/339/341 (12.50/ 7.29/9.08) was arised by the loss of HCl molecule from parent molecule $[(M+1)]^+$. The set of peaks at m/z 235/237/239 (35.42/20.83/8.34) $[(p\text{-}ClC_6H_5)_2CH]^+$ was obtained by the cleavage of 2-3 bond. The mode of fragmentation is showed in **CHART-19**. The ^{1}H-NMR **(FIG. 59)** and ^{13}C-NMR **(FIG. 60)** spectra of **R** dissolved in $CDCl_3$ showed signals as assigned **(TABLE-20)**. The assignments of all ^{1}H-NMR and ^{13}C-NMR signals to

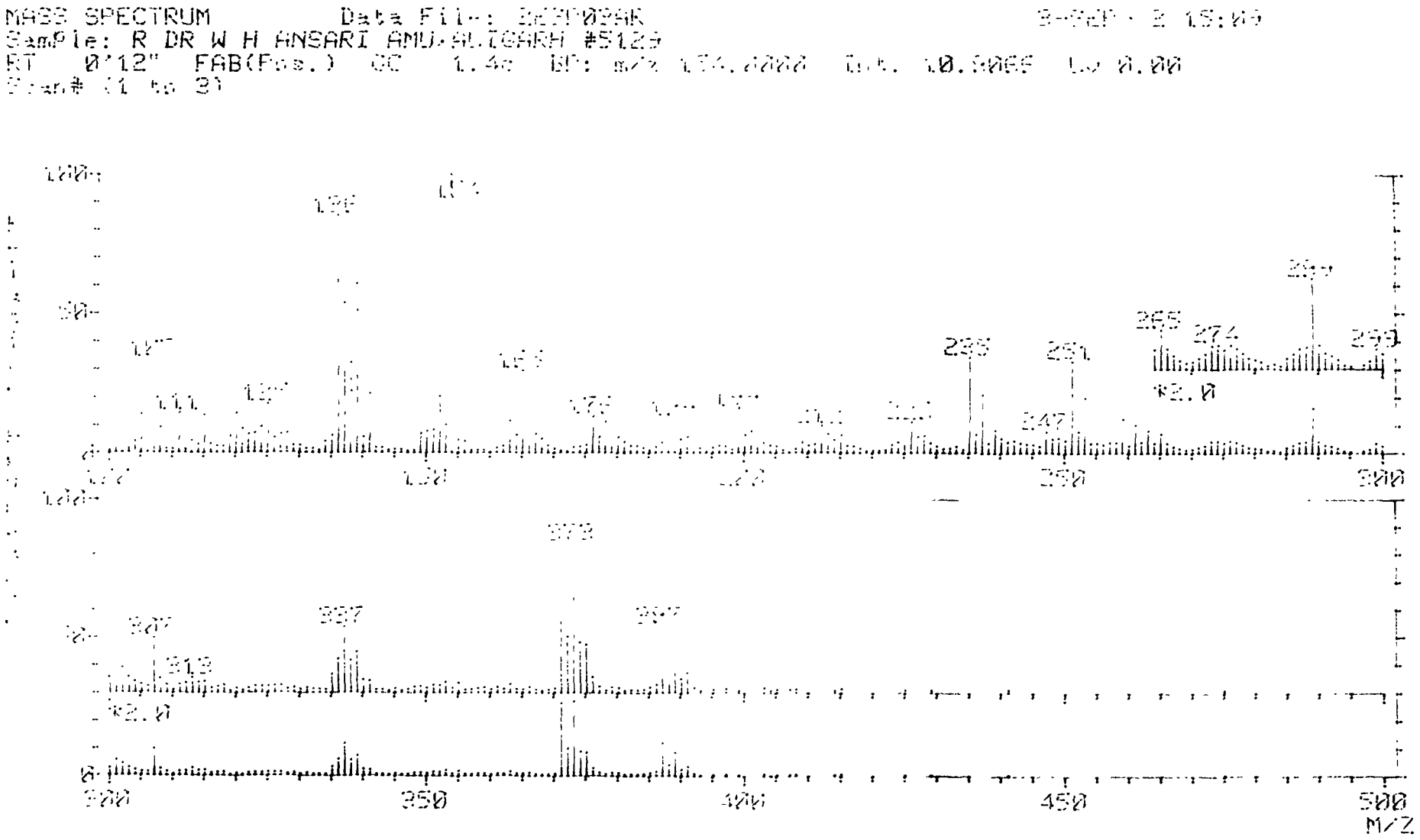

MASS SPECTRUM
Sample: R DR W H ANSARI AMU-ALTOARH #5125
RT 0'12" FAB(Pos.)
Scan# (1 to 3)
235
251
265
274
247
313
337
273
350
400
450
500
M/Z

FIG. 58

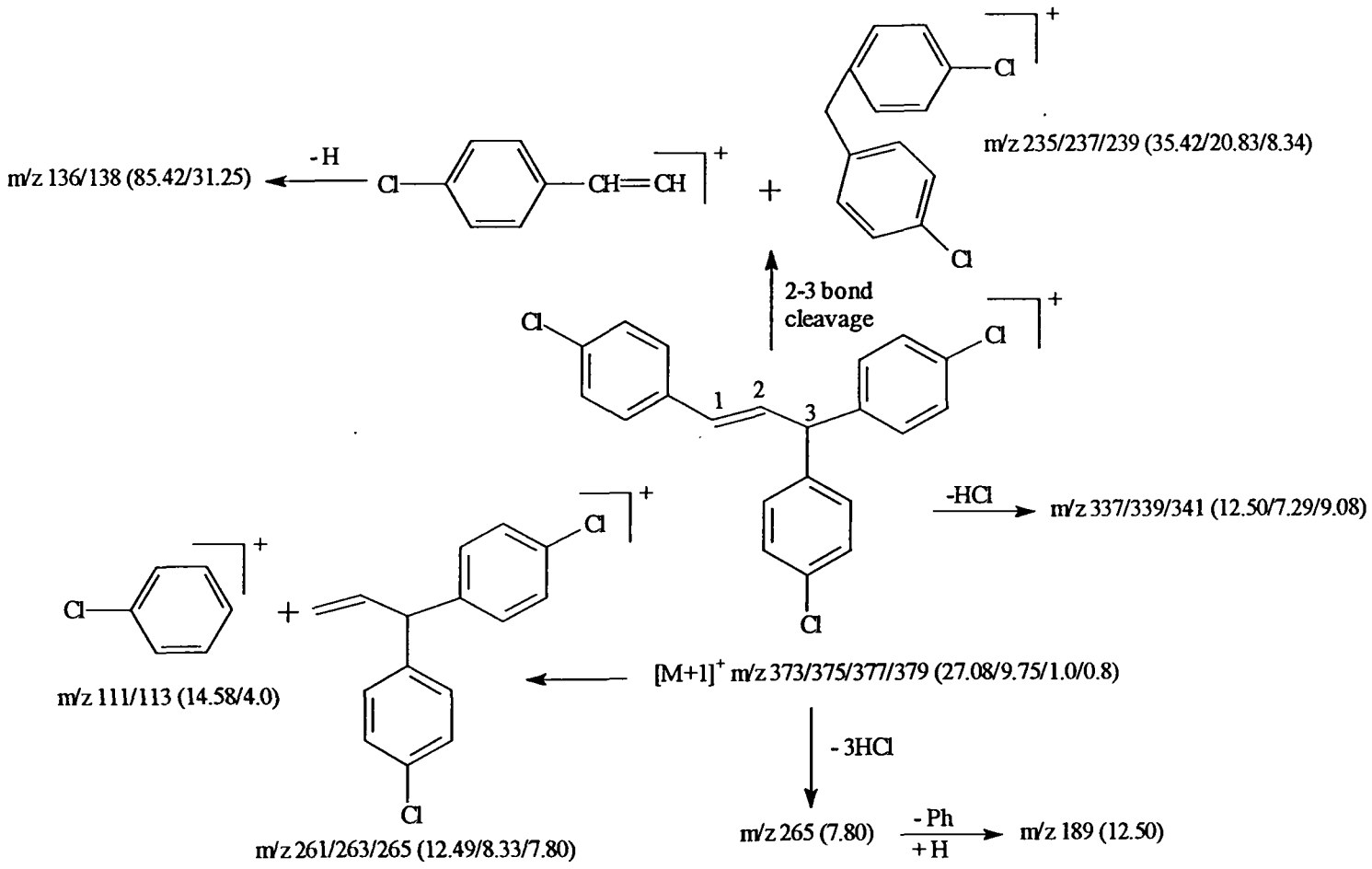

m/z 136/138 (85.42/31.25)
-H
Cl
CH=CH
+
Cl
m/z 235/237/239 (35.42/20.83/8.34)
2-3 bond cleavage
Cl
1
2
3
Cl
-HCl
m/z 337/339/341 (12.50/7.29/9.08)
Cl
m/z 111/113 (14.58/4.0)
+
Cl
Cl
[M+1]+ m/z 373/375/377/379 (27.08/9.75/1.0/0.8)
- 3HCl
m/z 261/263/265 (12.49/8.33/7.80)
m/z 265 (7.80)
- Ph
+ H
m/z 189 (12.50)

CHART - 19

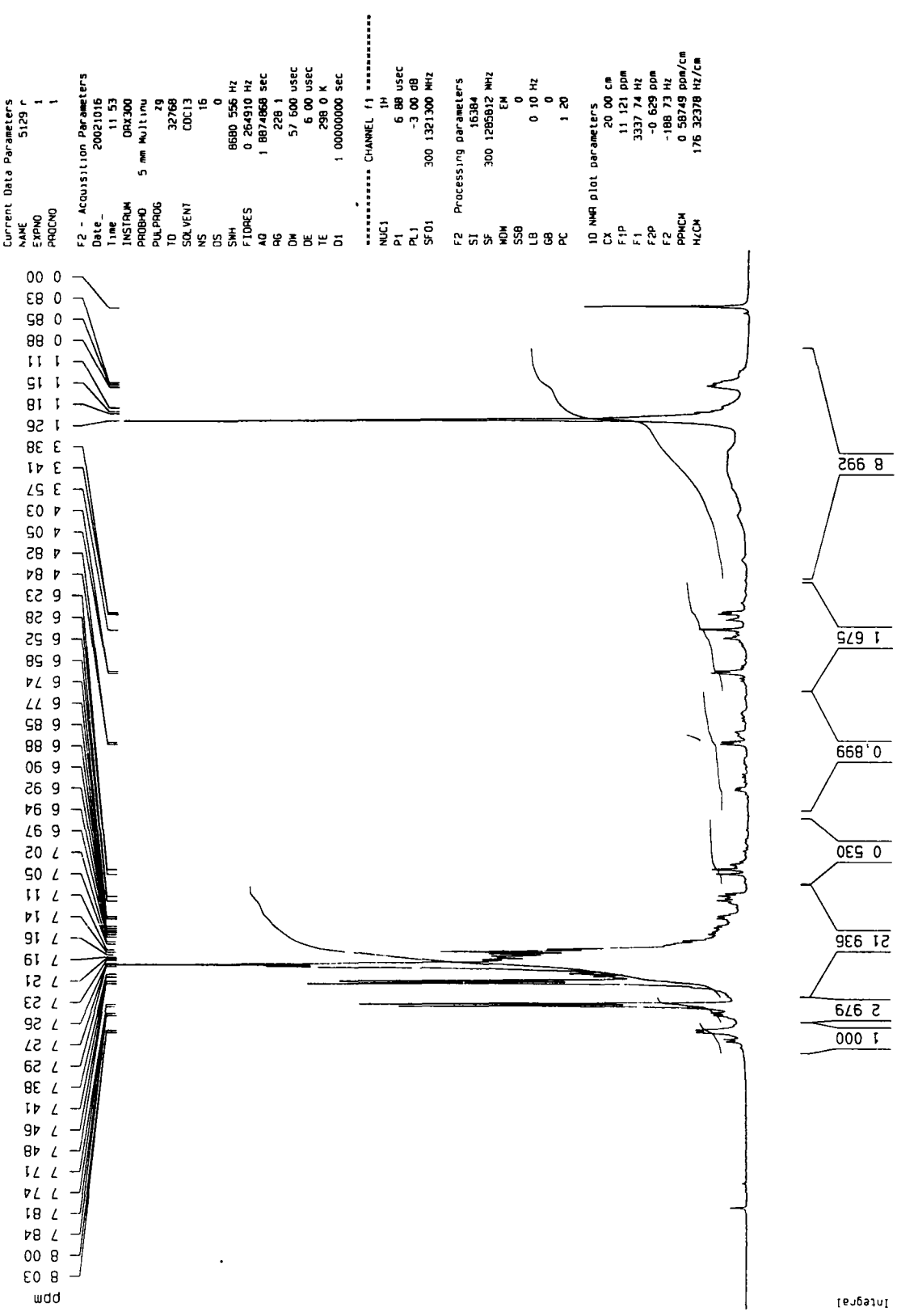
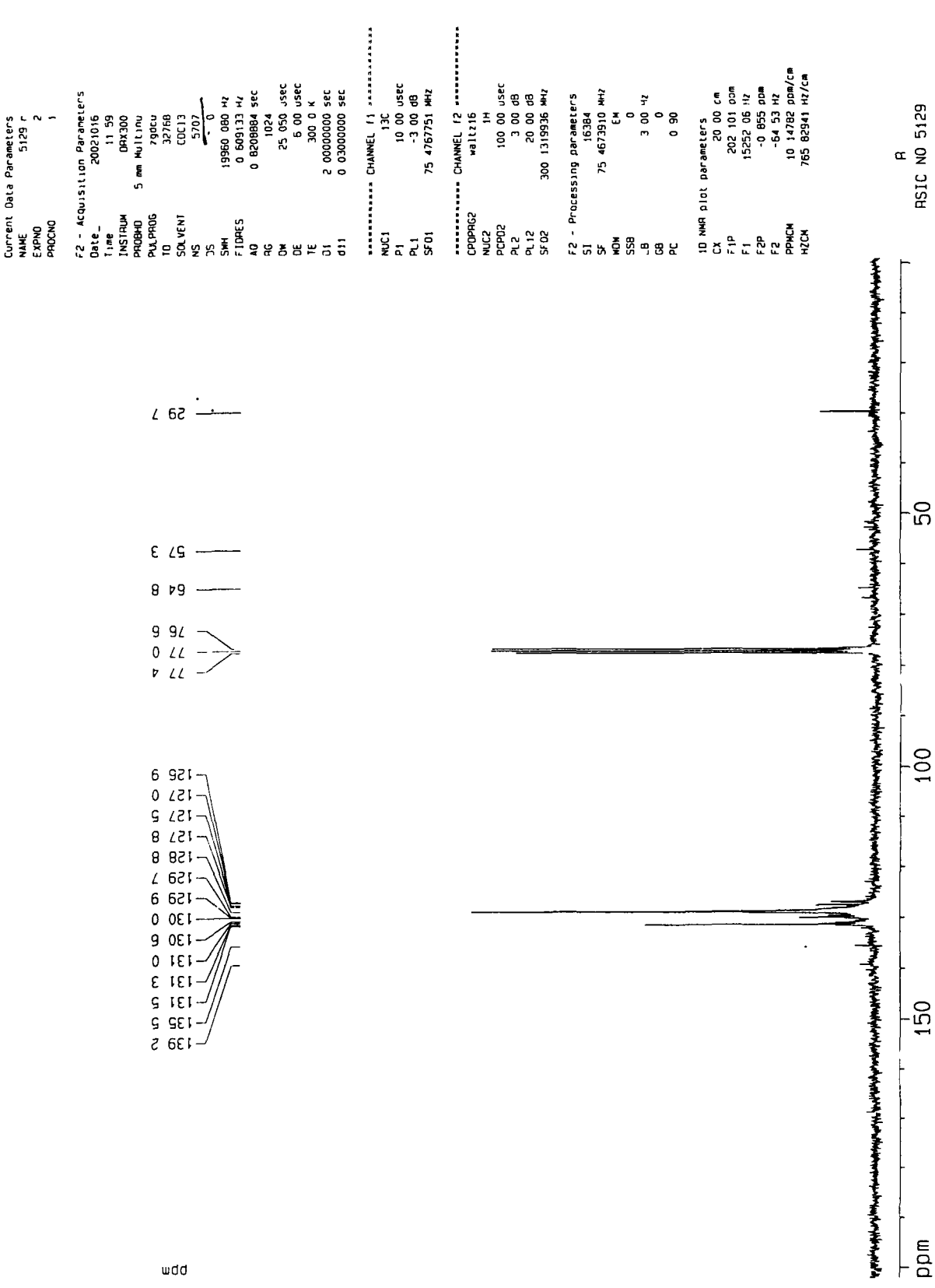

Current Data Parameters
NAME 5129 r
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20021016
Time 11 53
INSTRUM DRX300
PROBHD 5 mm Multinu
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 16
DS 0
SWH 8680 556 Hz
FIDRES 0 264910 Hz
AQ 1 8874868 sec
RG 228 1
DW 57 600 usec
DE 6 00 usec
TE 298 0 K
D1 1 00000000 sec
CHANNEL f1
NUC1 1H
P1 6 88 usec
PL1 -3 00 dB
SFO1 300 1321300 MHz
F2 Processing parameters
SI 16384
SF 300 1285812 MHz
WDW EM
SSB 0
LB 0 10 Hz
GB 0
PC 1 20
1D NMR plot parameters
CX 20 00 cm
F1P 11 121 ppm
F1 3337 74 Hz
F2P -0 629 ppm
F2 -188 73 Hz
PPMCM 0 58749 ppm/cm
HzCM 176 32378 Hz/cm
ppm
Integral
8 992
1 675
0 899
0 530
21 936
2 979
1 000
A
RSIC NO 5129

FIG. 59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P1 10 00 usec
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SF01 75 4767751 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100 00 usec
PL2 3 00 dB
PL12 20 00 dB
SF02 300 1319936 MHz
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SF 75 4673910 MHz
WDW EM
SSB 0
LB 3 00 Hz
GB 0
PC 0 90
1D NMR plot parameters
CX 20 00 cm
F1P 202 101 ppm
F1 15252 06 Hz
F2P -0 855 ppm
F2 -64 53 Hz
PPMCM 10 14782 ppm/cm
HZCM 765 82941 Hz/cm
A
RSIC NO 5129
ppm
50
100
150
77 4
77 0
76 6
64 8
57 3
29 7
139 2
135 5
131 5
131 3
131 0
130 6
130 0
129 9
129 7
128 8
127 8
127 5
127 0
125 9

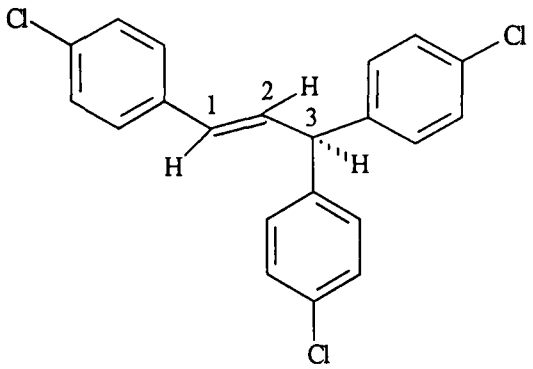
FIG. 60

TABLE - 20 : ^{1}H-NMR and ^{13}C-NMR spectral data of R (26)

H-nr	δ (ppm) .	Inte-gration	multi-plicity	J(Hz)	C-nr	δ (ppm)
1	7.16	1H	d	$J_{1,2}$ = 16.20	1	129.70
2	6.55	1H	dd	$J_{1,2}$ =16.20, $J_{2,3}$=7.20	2	130.60
3	4.82	1H	d	$J_{2,3}$=7.20	3	57.30
3 x Ar	7.11-7.84	12H	br m	–	3 x Ar	126.90-140.20

individual H- and C-atoms have been performed on the basis of typical chemical shift values, multiplicity, relative integrations and by comparing the spectral data with compound **Q (25) (TABLE-19).** The ^{1}H-NMR spectrum of **R** exhibited a doublet at δ7.16 (J=16.20 Hz) and double doublets δ6.55 with large coupling constants (J=16.20 Hz, J=7.20 Hz) assigned to protons at C-1 and C-2. The large coupling constant (J=16.20 Hz) of vicinal protons confirmed their trans geometry. The proton at C-1 appeared at lower field (δ7.16) as compared to proton at C-2 (δ6.55) because of deshielding effect of the aryl group attached to it. A doublet at δ4.82 (J=7.20 Hz) was assigned to methine proton at C-3. The signals for aromatic protons appeared as δ7.11-δ7.84 and were accounted for 12 protons (three aromatic rings). The ^{13}C-NMR signals were fully in agreement with the assigned structure. A signal observed at δ57.3 was assigned to C-3 carbon. The signals at δ129.70 and δ130.60 were attributed to C-1 and C-2 carbons.

On the basis of these facts the structure of **R** was formulated as *1,3,3-tris(4-chlorophenyl)prop-1-ene (26)*.



R (26)

Experimental

EXPERIMENTAL

4,4'-Dichlorochalcone (1)

Compound (1) was prepared exactly as reported in **CHAPTER-1**.

1,3,3-Tris(4-chlorophenyl)propan-1-one P (2)

Compound (2) was also prepared exactly as reported in **CHAPTER-1.**

1,3,3-Tris (4-chlorophenyl)propan-1-ol Q (25) (Reduction of P (2) with sodium borohydride)

A mixture of 1,3,3-tris(4-chlorophenyl)propan-1-one (2 gm, 0.0051 mol) and sodium borohydride (2.70 gm, 0.073 mol), in tetrahydrofuran (80 ml) was refluxed with 8 ml of 5% sodium hydroxide for 18 h. The progress of the reaction was monitored by TLC at every 30 minutes. After completion, the reaction mixture was concentrated under reduced pressure, extracted with ethyl acetate and washed with water several times until the solution was neutral. The ethyl acetate solution was then dried over Na_2SO_4. The solvent was evaporated and the coloured oily residue left was examined by TLC (silica gel 'G' pet. ether-benzene, 8:2 v/v) which revealed the presence of a major spot labelled as **Q**. The oily residue was then chromatographed over silica gel column using pet. ether-benzene 8:2 v/v as an eluent. Elution of the column furnished a white semi solid mass 1.73 gm (90.71%), R_f 0.836 (pet. ether-benzene, 8:2 v/v)

Spectral data of Q (25)

IR (KBr pellet) : υ_{max} : 3580 (OH), 2939, 2923 (CH), 1597, 1576 (phenyl), 1517, 1490, 1404, 1344, 1293, 1180, 1091, 1013, 960, 898, 832, 771, 754, 535, 722, 676, 568, 528.

^{1}H-NMR (acetone-d_6, 400 MHz) : δ_H :4.47 (1H, d, J=4.28 Hz, OH), 4.42 (1H, ddd, $J_{2up,1}$=8.85 Hz, $J_{2dn,1}$=9.01 Hz, $J_{1,OH}$=4.28 Hz, H-1), 2.32 (1H, ddd, $J_{2up,2dn}$=14.04 Hz, $J_{2up,3}$=5.65 Hz, $J_{2up,1}$=8.85Hz, H-2up), 2.46 (1H, ddd, $J_{2up,2dn}$=14.07 Hz, $J_{2dn,3}$=10.07Hz, $J_{2dn,1}$=9.01 Hz, H-2dn), 4.32 (1H, dd, $J_{2up,3}$=5.65 Hz, $J_{2dn,3}$=10.07 Hz, H-3), 7.20-7.50 (12H, b rm, 3xH-Ar).

^{13}C-NMR (acetone-d_6, 100 MHz) : δ_C : 71.17 (C-1), 45.92 (C-2), 47.24 (C-3), 124.11-145.79 (3xC-Ar).

DCI-MS (NH_3 as reagent gas) : m/z 390/392/394 (17.07/14.63/2.44), 372/374 (2.44/2.40), 337/339/341 (24.40/21.95/2.40), 235/237/239 (100.0/60.5/11.3), 155/157 (8.5/2.40), 151 (8.5), 140 (8.3), 139 (22.5), 138 (4.6), 137 (5.9), 134 (5.6), 128 (4.8), 125 (5.2), 118 (6.2), 117 (19.0), 109 (5.4), 108 (13.6), 107 (4.8), 99 (7.0), 94 (4.7), 93 (6.2), 92 (5.7), 91 (15.6), 82 (5.1), 77 (8.1), 76 (20.7).

1,3,3-Tris(4-chlorophenyl)prop-1-ene R (26) [Dehydration of Q (25) in the presence of *p*-toluenesulphonic acid]

To a solution of 1,3,3-tris(4-chlorophenyl)propan-1-ol **Q (25)** (1.20 gm, 0.0031 mol) in dry benzene (25ml) was added *p*-toluenesulphonic acid (10 mg) and refluxed with stirring over an oil bath at 80 °C for 4 h. The progress of the reaction was monitored by TLC at every 30 minute. After completion, the reaction mixture was concentrated, extracted with diethyl ether, washed with water and the organic phase dried over Na_2SO_4 overnight. Evaporation of solvent gave a white residue, which on TLC examination (silica gel 'G' benzene-diethyl ether, 9:1 v/v) showed the presence of a single spot, labelled as **R**. The product was recrystallized from benzene-acetone furnished **R** as white crystalline globules, 0.9723 gm (85%), m.p. 220 °C, R_f 0.56 (benzene-diethyl ether, 9:1 v/v).

Spectral data of R (26)

^{1}H-NMR ($CDCl_3$, 300 MHz) : δ_H : 7.16 (1H, d, $J_{1,2}$=16.20Hz, H-1), 6.55 (1H, dd, $J_{1,2}$=16.20Hz, $J_{2,3}$=7.20 Hz, H-2), 4.82 (1H, d, $J_{2,3}$=7.20 Hz, H-3), 7.11-7.84 (12H, br m, 3xH-Ar).

^{13}C-NMR ($CDCl_3$, 75 MHz) : δ_C : 129.70 (C-1), 130.60 (C-2), 57.3 (C-3), 126.90-140.20 (3 x C-Ar).

FAB-MS (Argon/Xenon, 6KV, 10mA, as the FAB gas) : m/z 373/375/377/379 (27.08/9.75/1.0/0.80), 337/339/341 (12.5/7.29/9.08), 307 (10.40), 289/291/293 (15.26/3.12/1.0), 261/263/265 (12.49/8.33/7.80), 251/253 (33.30/19.80), 247/249 (8.34/4.0), 235/237/239 (35.42/20.83/8.34), 226/228 (20.83/8.34), 212/214 (10.42/4.0), 199/201 (16.66/8.34), 189/191 (12.50/6.25), 176/178 (12.50/10.42), 165/167 (29.16/6.25), 154 (100), 141 (20.83), 139 (60.42), 138 (31.25), 137 (54.16), 136 (85.42), 125 (16.66), 120 (14.58), 115 (12.50), 113 (4.0), 111 (14.58), 107 (33.30).

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Chapter - 5

A Flavone from 1,3-Diketone (Baker-Venkataraman Transformation of 2-Benzoyloxyacetophenone) as an Undesired product in the Synthesis of Dithiazolidin-4-one

Theoretical

THEORETICAL

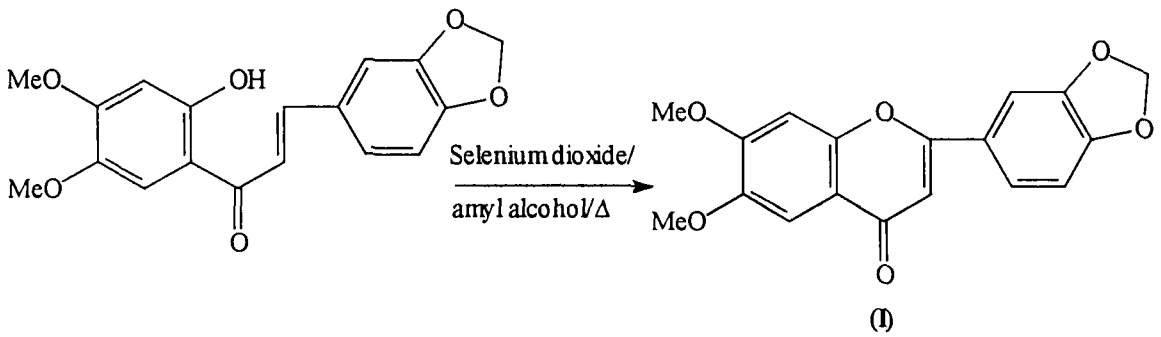
Flavonoids are widely distributed plant secondary metabolites and the field of flavonoids is one of the most fascinating area of plant chemistry. Their occurrence in nature, the chemical and biological relationship between them and the chemistry of their derivatives have been the subject of intensive study in recent past. These natural heterocyclic compounds possess a wide range of physiological and pharmacological properties, which have potential of being exploited for therapeutic purposes. Hundreds of new flavonoids and their derivatives are being discovered every year from natural sources and many of them have been synthesized. The study of their synthesis, stereochemistry and physiological activities continue to enhance the horizone of this field. Numerous physiological activities have been attributed to flavonoids[1]. Flavones and their derivatives have a variety of biological properties such as fish toxicity[2], heart stimulant[3], antiviral[4-5], antifungal[6], antihemolytic activity[7], anthelmintic activity[8], contraceptive drugs[9], vitamin P activity[10], antihistaminic activity[11], antihypertensive[12], analgesic and bronchodilator effects[13]. In addition, they inhibit lipid peroxidation[5,14] platelet aggregation[15], antiinflammatory[5,16], antiallergic[5,16,17], antibacterial[16,18], antitumour[19] and coronary vasodilatory actions[16,17,20] and the activity of enzyme systems including cyclooxygenases and lipooxygenases[21]. Flavonoids having heterocyclic nucleus in place of one of the phenyl nucleus possess muscular relaxation effect[33], spasmolytic activity[24,25], flavonoids also exert effects as antioxidants, free radical scavengers and chelators of divalent cation[5].

Flavonoids play interesting role in arresting the growth of cancer and modulating cancer related process in cells. Protection against carcinogenecity of benzo[a]pyrene on the mouse skin has been observed with

quercetin and myricetin[26]. Putin and Morin have also been shown to be antitumourigenic[27]. Two important properties of flavonoids are their ability to inhibit cytochrome P450 monooxygenase activity and their selection induction of detoxification enzymes such as glutathione transferase, glucoronyl transferase, exposited hydrolase and quinone reductase[27]. Flavone-acetic acid, a synthetic flavonoid has been clinically evaluated for anticancer properties and found to be curative against a variety of transplantable murine tumours. Its action resembles that of tumour necrosis factor (TNF)[29]. Brake *et al.*[30] have demonstrated inhibition of cancer cell invasion *in vitro* with a number of flavonoids. Several flavonoids inhibit the metabolic activation of the chemical carcinogenes benzo[a] pyrene and aflatoxin[31]. Numerous other reports have shown that flavonoids exhibit protective effects against a number of chemical mutagens and carcinogens[32].

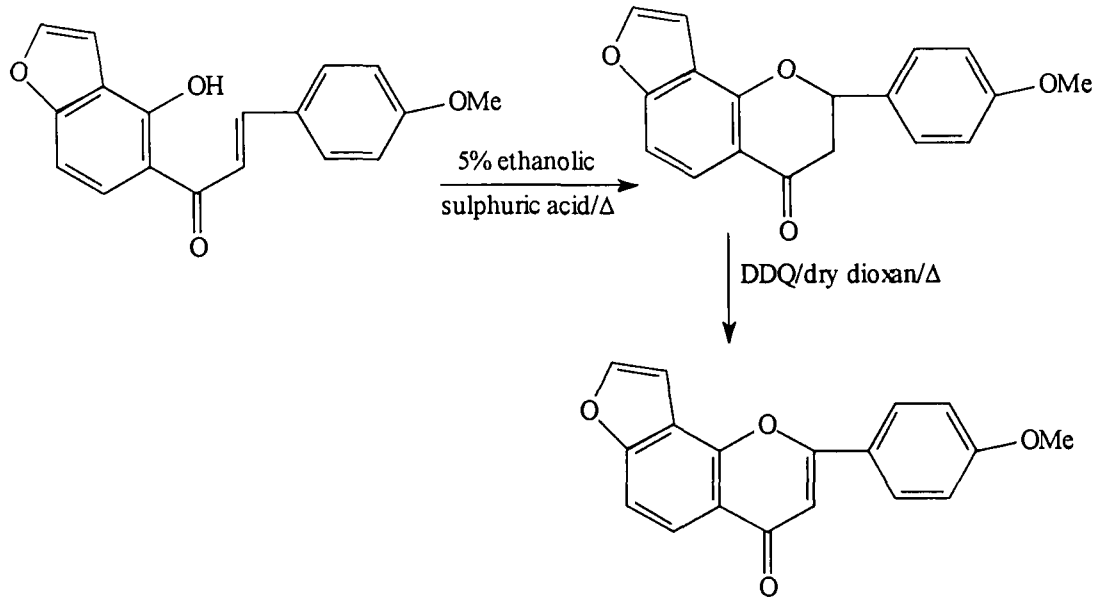
Several methods for the preparation of naturally occurring flavonoids have been reported in the literature[20].

A.C. Jain *et al.*[33-36] have reported the synthesis of 6,7-dimethoxy-3',4'-methylenedioxy flavone (**I**) by oxidation of 2'-hydroxy-4'5'-dimethoxy-3,4-methylenedioxy chalcone with selenium dioxide



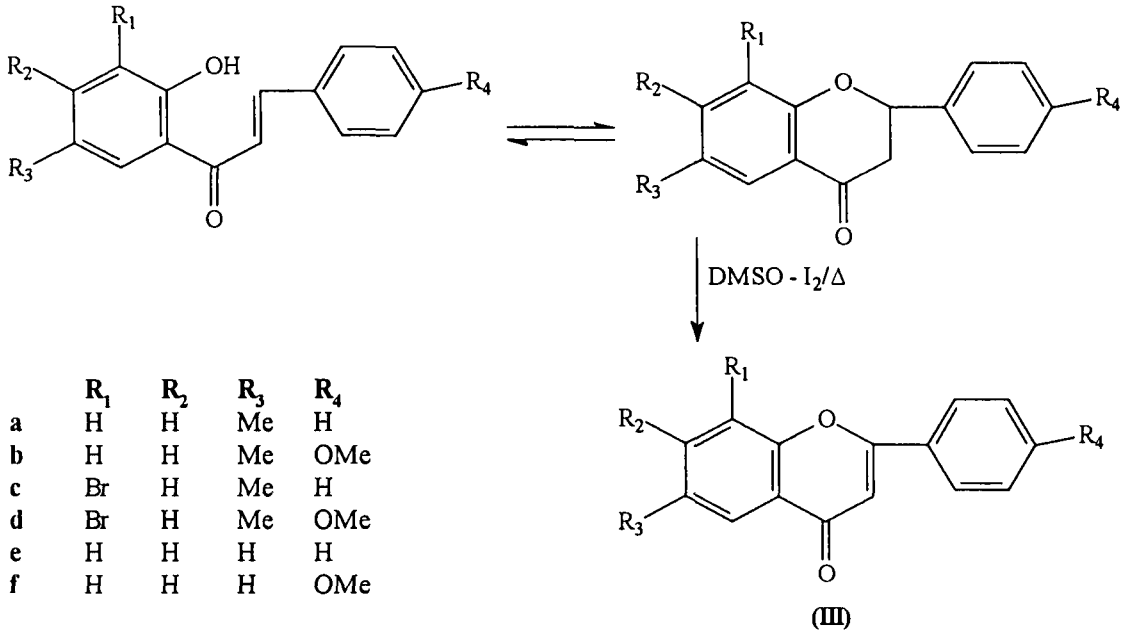
(I)

M. Krishnamurti *et al.*[37] have synthesized 4'-methoxyfurano[4",5" : 8,7] flavone (**II**) from 2'-hydroxy-4-methoxyfurano[4",5" : 3',4'] chalcone via 4'-methoxyfurano [4",5" : 8,7] flavanone with DDQ in dry dioxan.



(II)

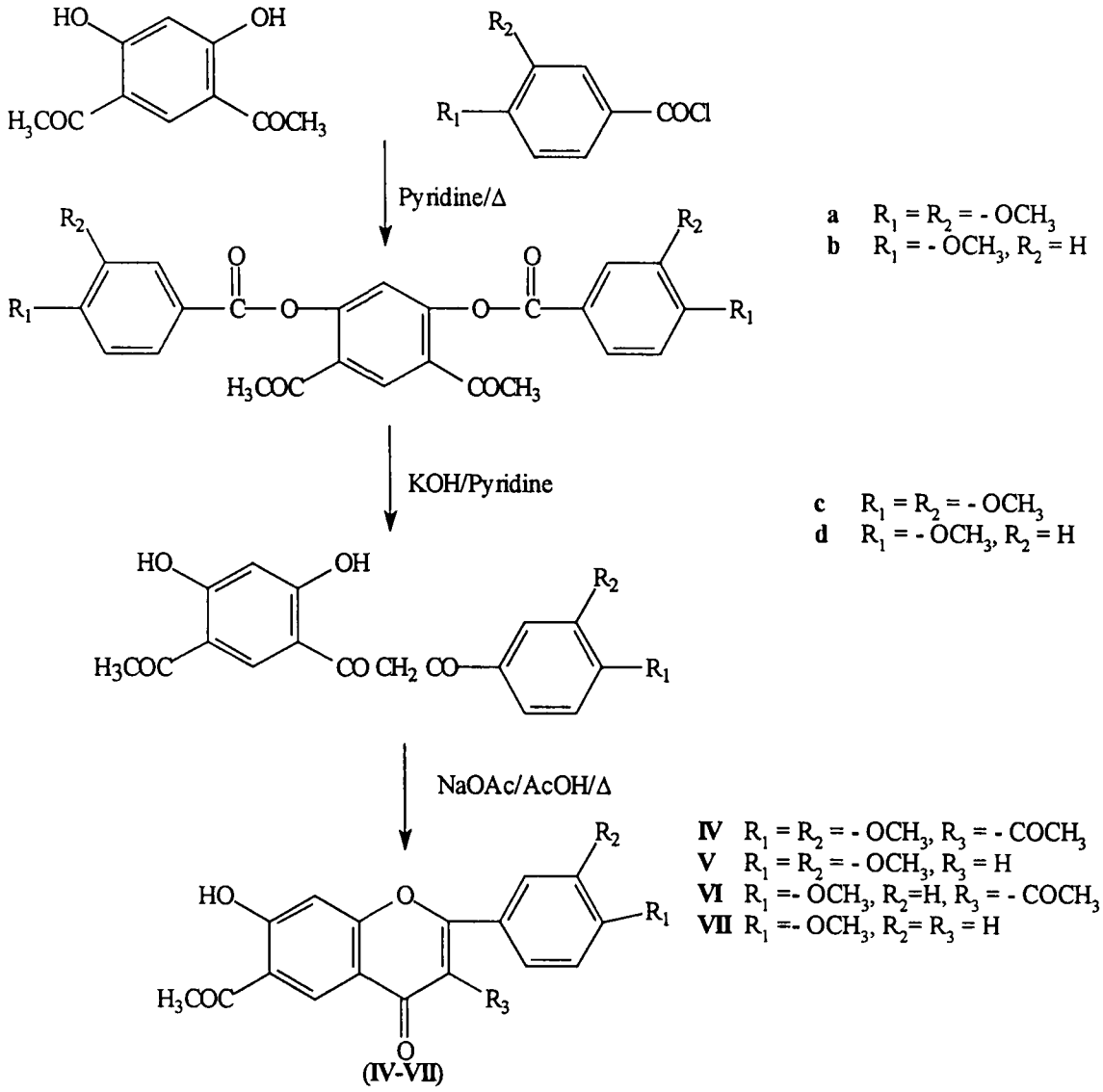
Also a number of substituted 2'-hydroxy chalcone have been converted into corresponding flavones by prolonged refluxing with SeO_2 in isoamyl alcohol[38] and is applicable in those chalcones which do not have free hydroxyl group other than at 2'-position. A.G. Doshi *et al.*[39] developed a new method, in which 2'-hydroxy chalcones or the isomeric flavones on refluxing in DMSO for 30 min. in presence of catalytic amount of iodine afforded the corresponding flavones **(III)**.



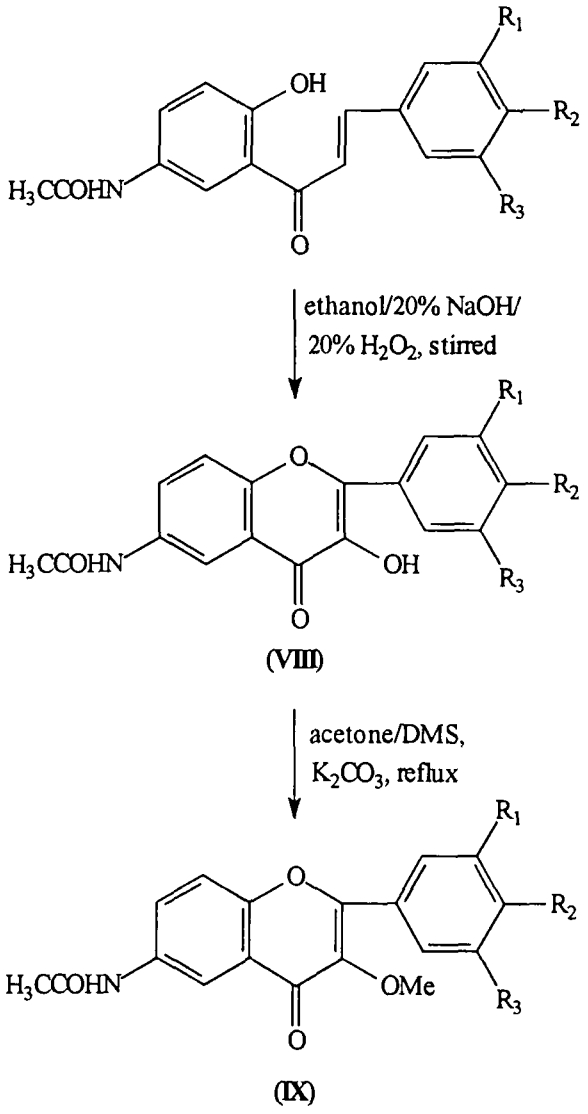
	R_1	R_2	R_3	R_4
a	H	H	Me	H
b	H	H	Me	OMe
c	Br	H	Me	H
d	Br	H	Me	OMe
e	H	H	H	H
f	H	H	H	OMe

(III)

P.E. Kumar *et. al.*[40] have synthesized a series of four new flavones, 3,6-diacetyl and 6-acetyl-7-hydroxy-3',4'-dimethoxy flavones **(IV-V)**, 3,6-diacetyl and 6-acetyl-7-hydroxy-4'-methoxy flavones **(VI-VII)** from 5-acetyl-2-4-diaroyl-dioxyacetophenone derivatives by Baker-Venkatraman rearragnement followed by acid cyclisation and deacetylation reaction.

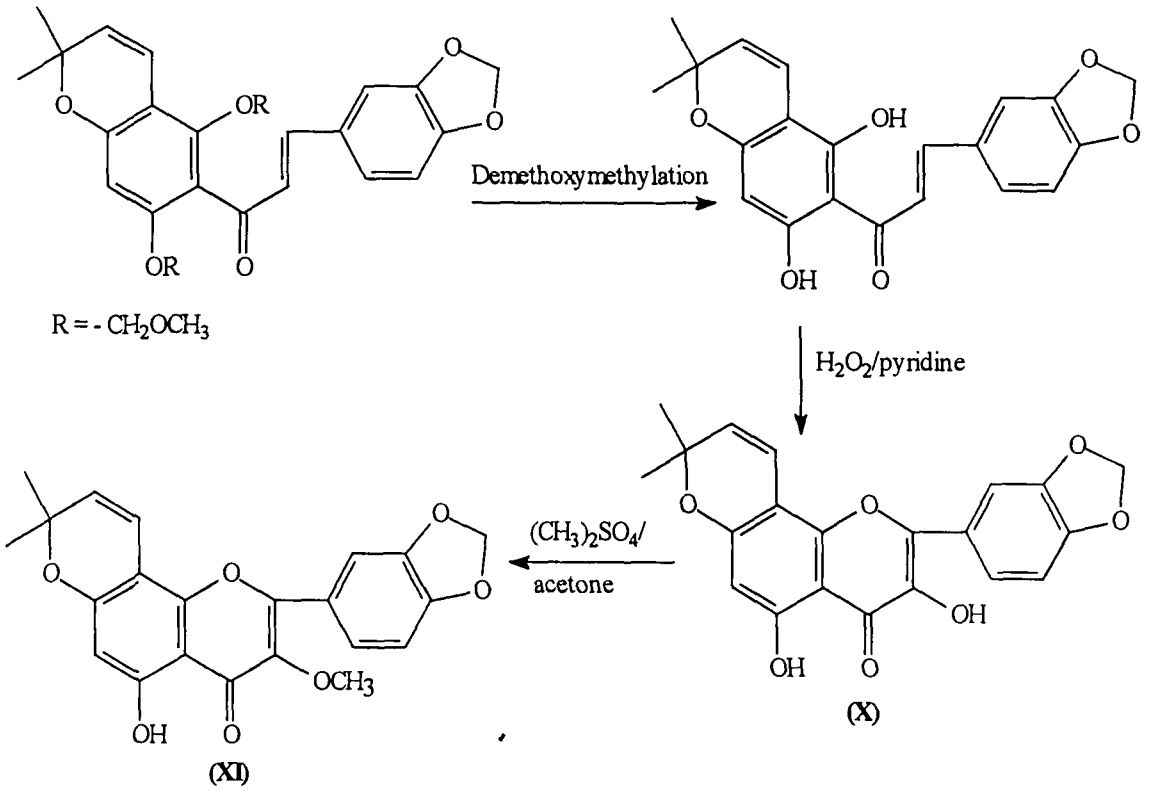


Recently R.B. Palkar *et al.*[41] have reported several naturally occurring flavones bearing a methoxy group at position 3 such as 4'-hydroxy-3-methoxy flavone for their antiviral activity and anti bacterial activity. Different 6-acetamido-3-hydroxy flavones (**VIII**) and 6-acetamido-3-methoxyflavones (**IX**) were synthesized from 5'-acetamido-3-aryl-2'-hydroxy chalcones.



	R_1	R_2	R_3
a	H	Cl	H
b	H	$N(CH_3)_2$	H
c	OMe	OMe	H
d	OMe	OMe	OMe

M. Amzad Hossain[42] have prepared 3,5-dihydroxy-3',4'-methylenedioxy-6", 6"-dimethylpyrano [2",3" : 7,8] flavone (**X**) and 3-methoxy-5-hydroxy-3,4-methylenedioxy-6", 6"-dimethylpyrano[2",3" : 7,8]flavone (**XI**) from 2', 6'-di(methoxymethoxy)-3',4'-methylene dioxy-6",6"-dimethylpyrano [2",3" : 4,3'] chalcone.



Discussion

DISCUSSION

SUMMARY

The work described in this chapter consists of the synthesis of -

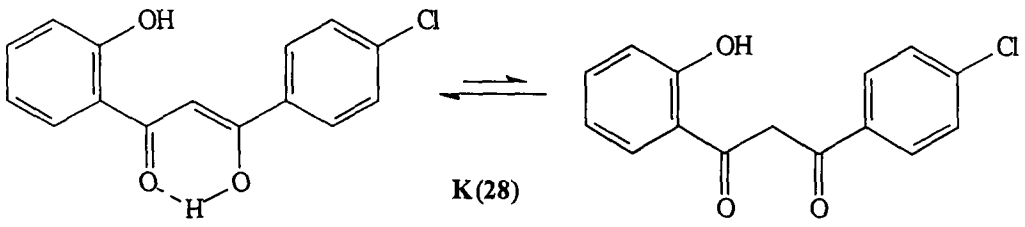
(i) 2-hydroxy-4'-chlorodibenzoylmethane ***K (28)*** *by Baker-Venkataraman transformation of 2-(4'-chlorobenzoyloxy)acetophenone as intermediate obtained from o-hydroxyacetophenone and p-chlorobenzoic acid in the presence of* $POCl_3$.

(ii) 4'-chloroflavone ***SD (29)*** *from 2-hydroxy-4'-chlorodibenzoylmethane* ***K (28)*** *as an undesired product, when the reaction was carried out with thioglycollic acid and ammonium carbonate in benzene to get dithiazolidin-4-one.*

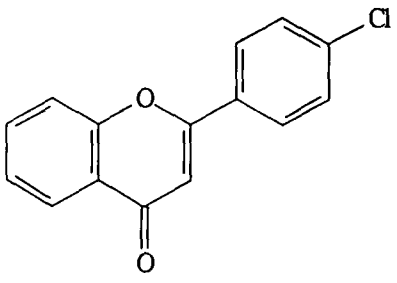
Structures are established on the basis of Mass, ^{1}*H-NMR and* ^{13}*C-NMR spectral studies.*

INTRODUCTION

In previous chapters we have synthesized 2-substituted 4-thiazolidinones as novel compounds from chalcones via their monoketo adducts using thioglycollic acid in the presence of ammonium carbonate in dry benzene. The aim of the present problem is to synthesize dithiazolidin-4-ones from 1,3-diketones using the same reagents. For this purpose, the precursor, 1,3-diketone **K (28)** is first prepared by Baker-Venkataraman transformation of 2-(4'-chlorobenzoyloxy)acetophenone obtained by the reaction of *o*-hydroxyacetophenone with *p*-chlorobenzoic acid in the presence of $POCl_3$. It is then reacted with thioglycollic acid and ammonium carbonate in dry benzene which yielded a flavone **K (29)** instead of the target compound, dithiazolidin-4-one. The ring closure of 1,3-diketone in acid medium to form flavone molecule is a well known reaction[44,45]. From ^{1}H-NMR spectrum, it is found that the 1,3-diketone exists in the equilibrium mixture of keto-enol tautomeric forms.



K(28)



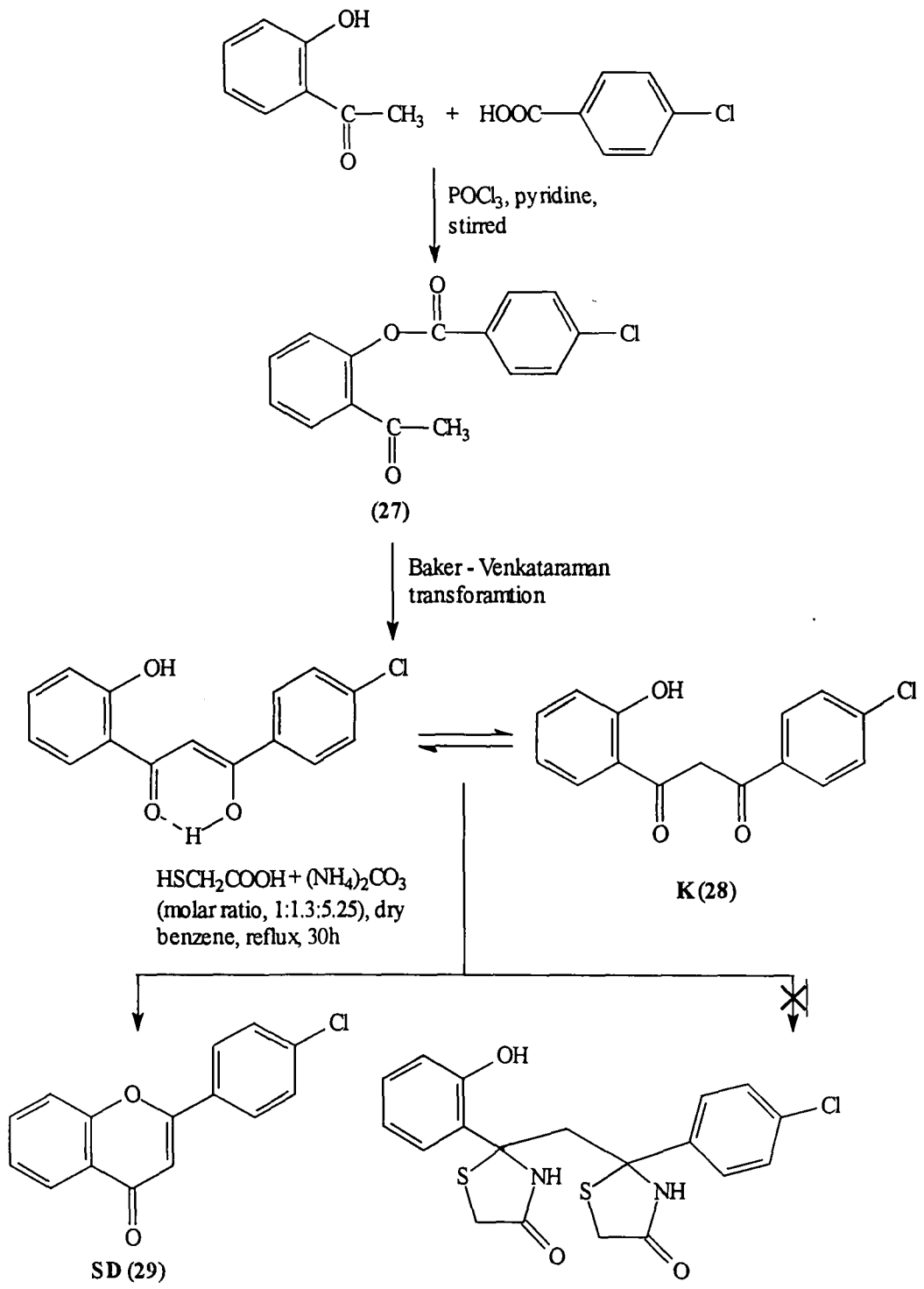
SD (29)

RESULTS AND DISCUSSION

The reaction was carried out in two steps as follows **(SCHEME-VIII)** :

The 1,3-diketone, 2-hydroxy-4'-chlorodibenzoyl methane **K (28)** was first prepared by Baker-Venkataraman transformation of 2-(4'-chlorobenzoyloxy) acetophenone condensing *o*-hydroxyacetophenone with *p*-chlorobenzoic acid (molar ratio, 1:1) in the presence of a catalytic amount of $POCl_3$. The crude product was washed with 10% $NaHCO_3$ solution and then crystallized from ethanol to yield **(28)** in 60% yield.

The 2-hydroxy-4'-chlorodibenzoyl methane **K (28)** was then condensed with thioglycollic acid and ammonium carbonate (molar ratio, 1:1.30:5.25) by refluxing in dry benzene for 30 h. The products on purification by column chromatography over silica gel using pet. ether-diethyl ether as eluent followed by crystallization afforded **SD (29)** as white crystalline needles in 80% yield. The target compound dithiazolidin-4-one could not be obtained. The 1,3-diketone did not react with thioglycollic acid and ammonium carbonate, it simply cyclized to give a flavone which is a well known cyclization reaction in acidic medium.


OH
C—CH3
O
+ HOOC
Cl
POCl3, pyridine,
stirred
O
O—C
Cl
C—CH3
O
(27)
Baker - Venkataraman
transforamtion
OH
Cl
O
H
O
HSCH2COOH + (NH4)2CO3
(molar ratio, 1:1.3:5.25), dry
benzene, reflux, 30h
OH
Cl
O
O
K (28)
Cl
O
O
SD (29)
OH
Cl
S
NH
S
NH
O
O

SCHEME - VIII

Synthesis of 2-hydroxy-4'-chlorodibenzoyl methane K (28) [from *o*-hydroxyacetophenone and *p*-chlorobenzoic acid in the presence of $POCl_3$ via 2-(4'-chlorobenzoyloxy)acetophenone by Baker-Venkataraman transformation]

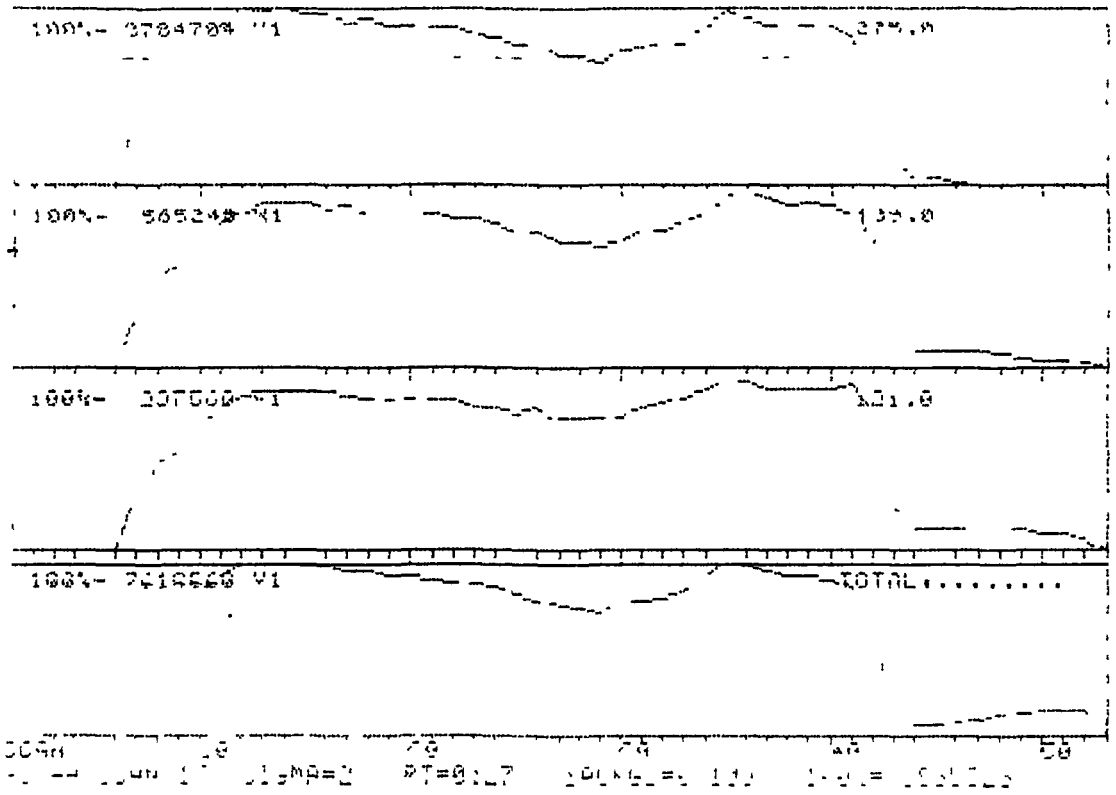
A solution of *o*-hydroxyacetophenone and *p*-chlorobenzoic acid (molar ratio, 1:1) in pyridine in the presence of $POCl_3$ was stirred at room temperature for 2 h. The reaction mixture on usual work up and recrystallization from ethanol, yielded 2-(4'-chlorobenzoyloxy)acetophenone as crystalline needles (65%) yield.

Baker-Venkataraman transformation

2-(4'-chlorobenzoyloxy)acetophenone was dissolved in pyridine and pulverized KOH (molar ratio, 1:2) was added to it with constant stirring. After completion, it was further stirred for 8 h. TLC examination (silica gel 'G' pet. ether-diethyl ether, 8:2 v/v) of the reaction mixture showed the presence of a brown spot labelled as **K**. After usual work up and crystallization from ethanol afforded **K (28)** as yellow crystalline needles in 60% yield.

Structure Elucidation of K (28)

It is a yellow needle shaped crystalline solid, m.p. 122 °C and appears dark brown on exposure to iodine vapours (TLC). The structure of **K** has been elucidated by DCI-MS, ^{1}H-NMR and ^{13}C-NMR spectra. The DCI-MS (NH_3 as reagent gas) of **K (28)** **(FIG. 61)** showed $[M+H]^+$ peaks as the base peak at m/z 275/277 (100.0/35.4), confirming its molecular weight as 274/276 [$C_{15}H_{11}O_3Cl$]. A set of peaks observed at m/z 139/141 (14.8/4.8) was due to the 2-3 bond cleavage. The important fragement ions are shown in **CHART-20**.



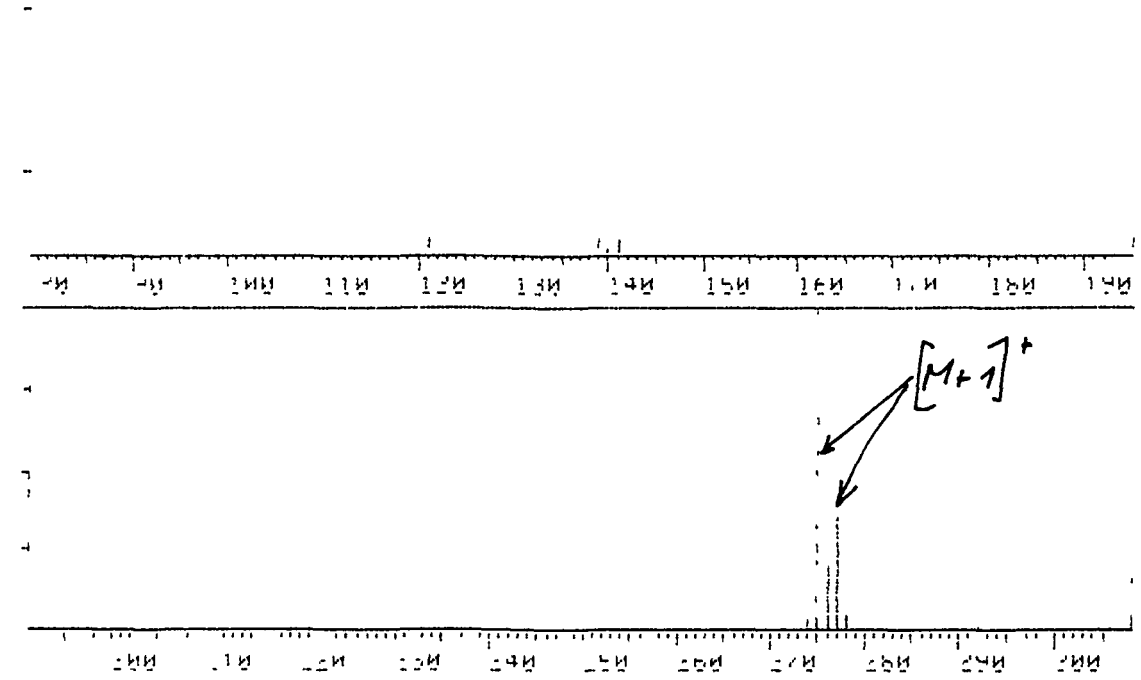


FIG. 61

```
SUY4A SCAN 17  SIGMA=2   RT=0.27   BACKGD=0X100   100%= 3555328
TITLE  DITETON13

  121 00      5 1     141 00      4 3     275 00    100 0     277 00     35 4
  139 00     14 8     274 00      3 4     276 00     20 2     278 00      6 3
```

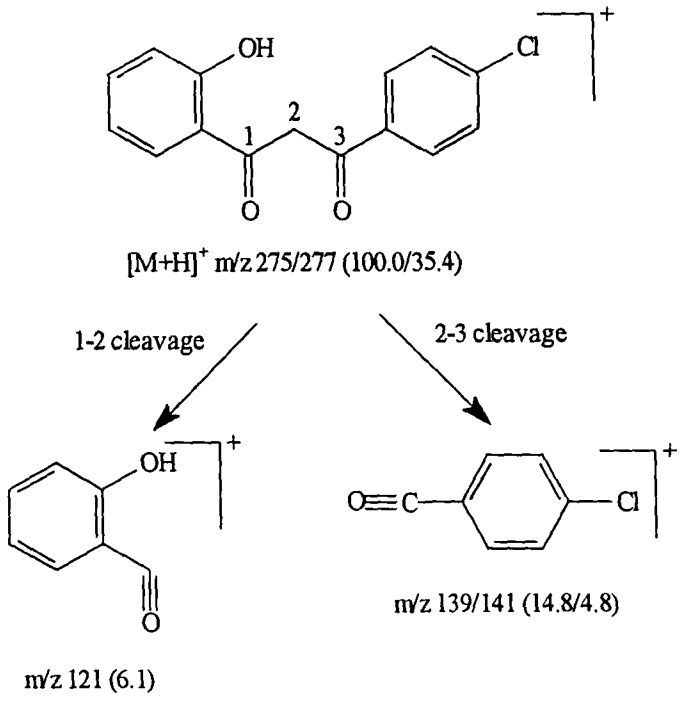


CHART - 20

The ^{1}H-NMR (**FIG. 62**) and ^{13}C-NMR (**FIG. 63**) spectra of **K** dissolved in acetone-d_6 showed signals as assigned in **TABLE-21**. The assignments of all ^{1}H-NMR and ^{13}C-NMR signals to individual H- and C-atoms have been performed on the basis of typical chemical shift values, multiplicity and relative integrations. The two singlets, one at δ4.91 and another at δ7.31 were attributed to the keto and enol forms. The other two singlets at δ11.88 and δ11.83 were assigned to aromatic and enolic hydroxyl groups. The aromatic protons signals were assigned as shown in **TABLE-21**. The ^{13}C-NMR spectrum showed signals as assigned (**TABLE-21**). The signals at δ50.26 was assigned to C-2_{keto} carbon and at δ94.01 to C-2_{enol} carbon. The ^{13}C-NMR spectrum of **K** showed the ring carbons signals 133.25 (C-Ar'-1), 163.25 (C-Ar'-2), 119.22 (C-Ar'-3), 137.09 (C-Ar'-4), 120.20 (C-Ar'-5), 130.51 (C-Ar'-6), 131.24 (C-Ar-1), 129.92 (C-Ar-2,6), 129.61 (C-Ar-3,5), 139.13 (C-Ar-4). The ^{13}C-NMR spectral data are thus in agreement with the assigned structure.

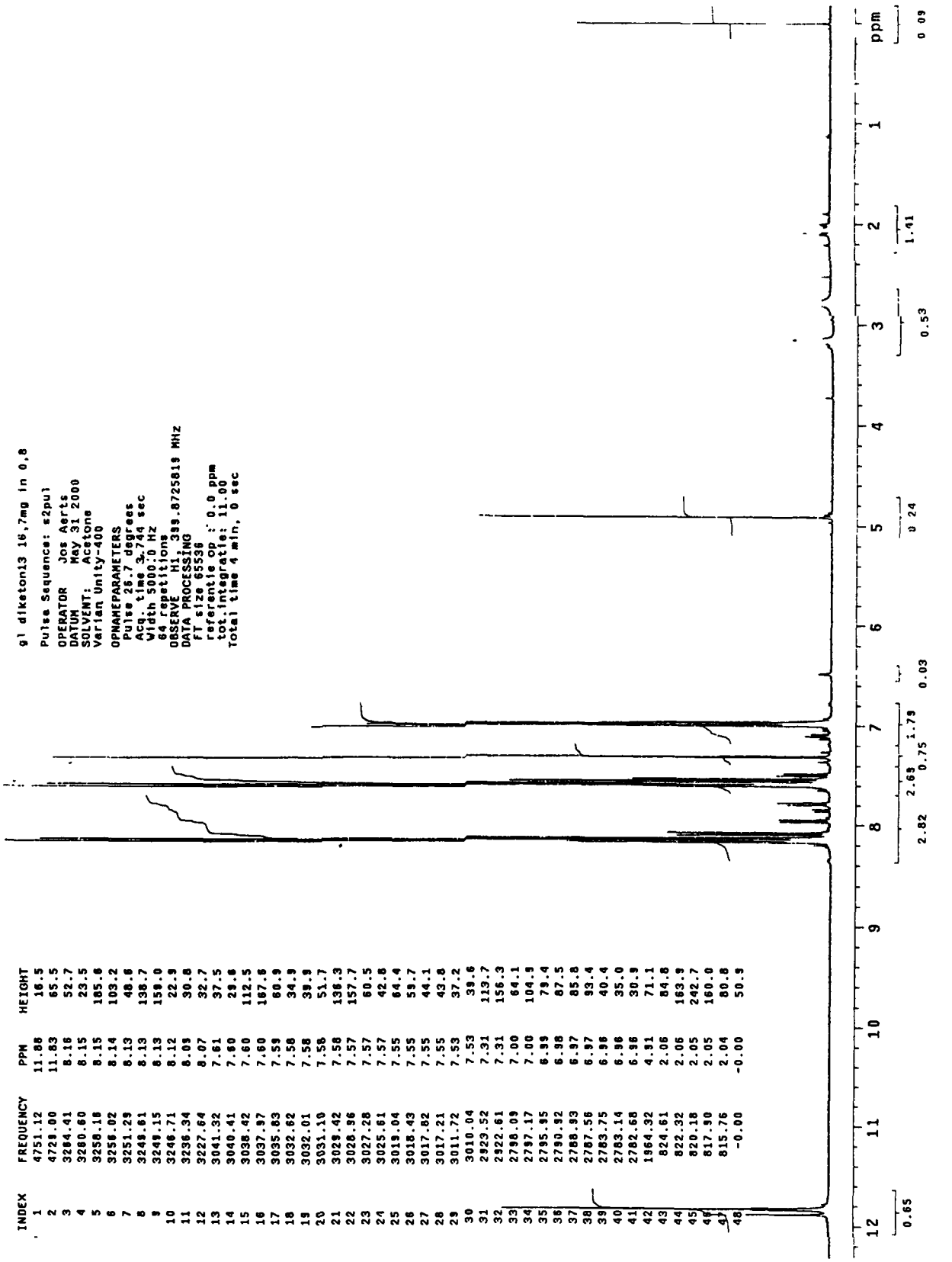

gl diketon13 16,7mg in 0,8
Pulse Sequence: s2pul
OPERATOR Jos Aerts
DATUM May 31 2000
SOLVENT: Acetone
Varian Unity-400
OPNAMEPARAMETERS
Pulse 26.7 degrees
Acq. time 3.744 sec
Width 5000.0 Hz
64 repetitions
OBSERVE H1, 399.8725819 MHz
DATA PROCESSING
FT size 65536
referentie op i: 0.0 ppm
tot.integratie: 11.00
Totai time 4 min, 0 sec
INDEX FREQUENCY PPM HEIGHT
1 4751.12 11.88 16.5
2 4728.00 11.83 65.5
3 3284.41 8.16 52.7
4 3280.60 8.15 23.5
5 3258.18 8.15 185.6
6 3256.02 8.14 103.2
7 3251.29 8.13 48.6
8 3249.61 8.13 138.7
9 3248.15 8.13 159.0
10 3246.71 8.12 22.9
11 3236.34 8.09 30.8
12 3227.64 8.07 32.7
13 3041.32 7.61 37.5
14 3040.41 7.60 29.6
15 3038.42 7.60 112.5
16 3037.97 7.60 187.6
17 3035.83 7.59 60.9
18 3032.62 7.58 34.9
19 3032.01 7.58 39.9
20 3031.10 7.58 51.7
21 3029.42 7.58 136.3
22 3028.96 7.57 157.7
23 3027.28 7.57 60.5
24 3025.61 7.57 42.6
25 3019.04 7.55 64.4
26 3018.43 7.55 59.7
27 3017.82 7.55 44.1
28 3017.21 7.55 43.6
29 3011.72 7.53 37.2
30 3010.04 7.53 39.6
31 2923.52 7.31 113.7
32 2922.61 7.31 156.3
33 2798.09 7.00 64.1
34 2797.17 7.00 104.9
35 2795.95 6.99 78.4
36 2790.92 6.98 87.5
37 2788.93 6.97 85.8
38 2787.56 6.97 93.4
39 2783.75 6.96 40.4
40 2783.14 6.96 35.0
41 2782.68 6.96 30.9
42 1964.32 4.91 71.1
43 824.61 2.06 84.8
44 822.32 2.06 163.9
45 820.18 2.05 242.7
46 817.90 2.05 160.0
47 815.76 2.04 80.8
48 -0.00 -0.00 50.9
ppm
2.82
2.68
0.75
1.79
0.03
0.24
0.53
1.41
0.09
0.65

FIG. 62

INDEX	FREQUENCY	PPM	HEIGHT	INDEX	FREQUENCY	PPM	HEIGHT
1	21292.00	211.76	-1.2	51	2940.46	29.24	88.4
2	20733.51	206.21	11.6	52	2919.86	29.04	3.2
3	20714.44	206.02	701.7	53	0.00	0.00	1.6
4	20694.60	205.82	12.0	54	-261.70	-2.60	-1.1
5	20677.05	205.64	2.6	55	-1864.68	-18.55	-1.4
6	20635.09	205.23	1.5				
7	20380.26	202.69	1.7				
8	19950.71	198.42	-1.2				
9	19788.20	196.80	13.3				
10	19517.35	194.11	1.9				
11	18200.48	181.01	-1.1				
12	17840.36	177.43	7.7				
13	16425.82	163.36	3.6				
14	16414.38	163.25	20.7				
15	14365.83	142.88	1.2				
16	14106.42	140.30	3.3				
17	13988.92	139.13	23.5				
18	13855.40	137.80	10.5				
19	13784.45	137.09	57.4				
20	13740.96	136.66	3.0				
21	13693.66	136.19	2.4				
22	13397.63	133.25	14.4				
23	13320.57	132.48	10.9				
24	13195.44	131.24	30.8				
25	13122.20	130.51	76.7				
26	13063.45	129.92	161.4				
27	13058.11	129.87	30.4				
28	13032.17	129.61	175.3				
29	12991.73	129.21	7.8				
30	12899.41	128.29	6.9				
31	12738.43	126.69	3.7				
32	12302.77	122.36	3.7				
33	12137497	120.72	2.2				
34	12086.09	120.20	76.6				
35	12079.99	120.14	14.3				
36	12057.86	119.92	15.3				
37	12004.46	119.39	4.4				
38	11987.67	119.22	83.4				
39	11955.63	118.90	13.2				
40	9452.35	94.01	65.5				
41	5856.50	58.25	-1.1				
42	5082.86	50.55	3.9				
43	5053.87	50.26	12.3				
44	4656.36	46.31	-1.2				
45	3056.43	30.40	89.3				
46	3036.59	30.20	261.0				
47	3017.52	30.01	539.0				
48	2998.44	29.82	613.4				
49	2978.61	29.62	530.6				
50	2959.53	29.43	273.				

```
gl diketon13 16,7mg in 0,8

Pulse Sequence: s2pul

OPERATOR    Jos Aerts
DATUM       May 31 2000
SOLVENT:    Acetone
Varian Unity-400

OPNAMEPARAMETERS
 Pulse 26.7 degrees
 Acq. time 1.199 sec
 Width 25000.0 Hz
 24000 repetitions
OBSERVE  C13, 100.5479460 MHz
DECOUPLE  H1, 399.8750067 MHz
 Power 37 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
 FT size 65536
 referentie op : 0.0 ppm
Total time 8 hr, 4 min, 4 sec
```

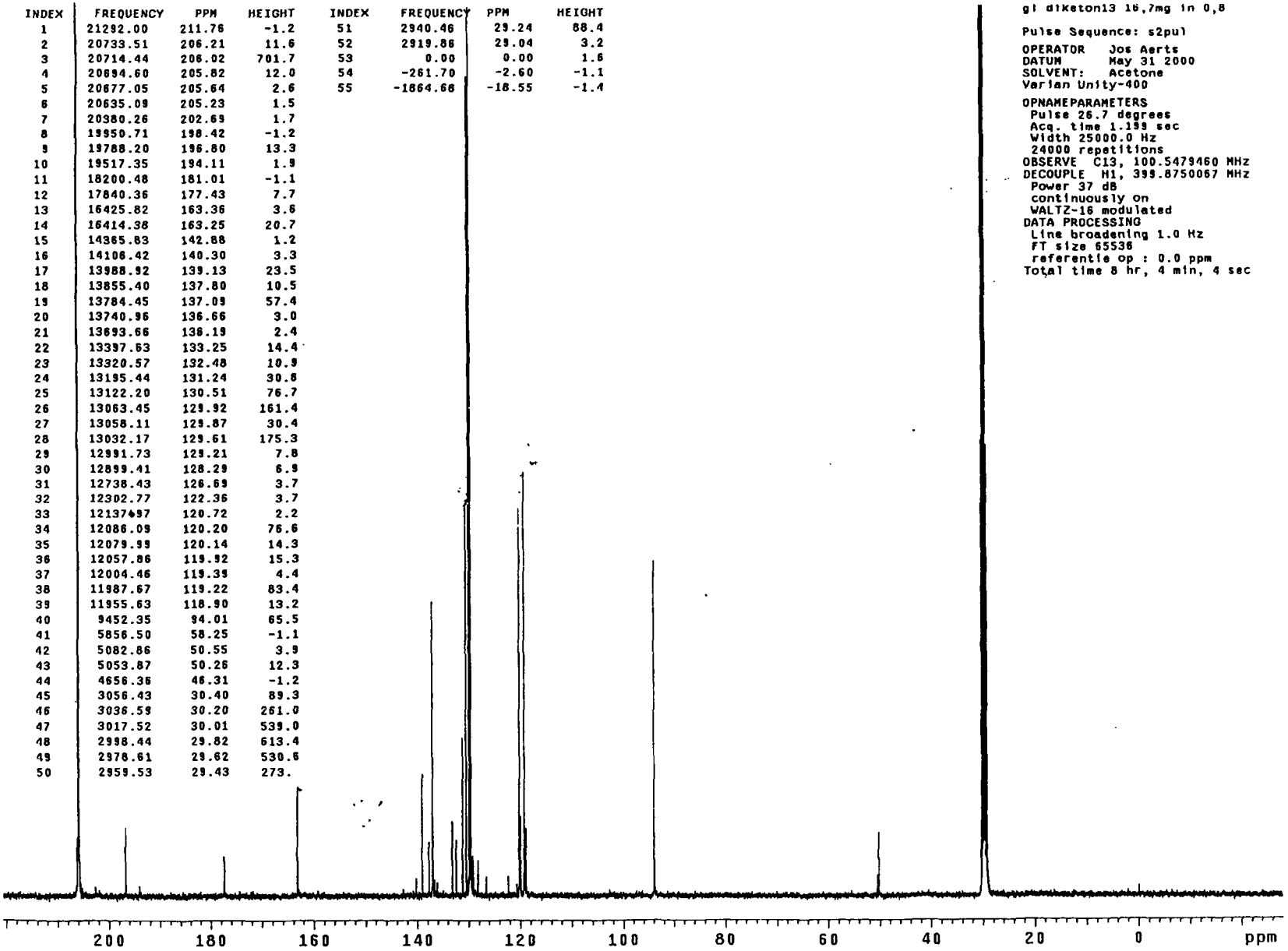


FIG. 63

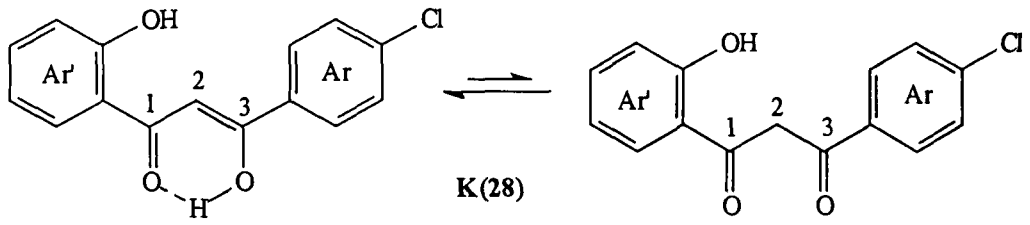
300

TABLE -21 : ^{1}H-NMR and ^{13}C-NMR spectral data of K (28)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)	C-nr	δ (ppm)
2_{keto}	4.91	2H	s	–	2_{keto}	50.26
2_{enol}	7.31	1H	s	–	2_{enol}	94.01
Ar'-OH	11.88	1H	s	–	$1_{enol}/1_{keto}$	196.80[a]
enolic OH	11.83	1H	s	–	$3_{enol}/3_{keto}$	177.43[a]
Ar'	7.00-8.15	4H	br m	–	Ar'-1	133.25
Ar-2,6	8.14	2H	d	$J_{Ar-2,6}$=8.55	Ar'-2	163.25
Ar-3,5	7.68	2H	d	$J_{Ar-3,5}$=8.55	Ar'-3	119.22
					Ar'-4	137.09
					Ar'-5	120.20
					Ar'-6	130.51
					Ar-1	131.24
					Ar-2,6	129.92
					Ar-3,5	129.61
					Ar-4	139.13

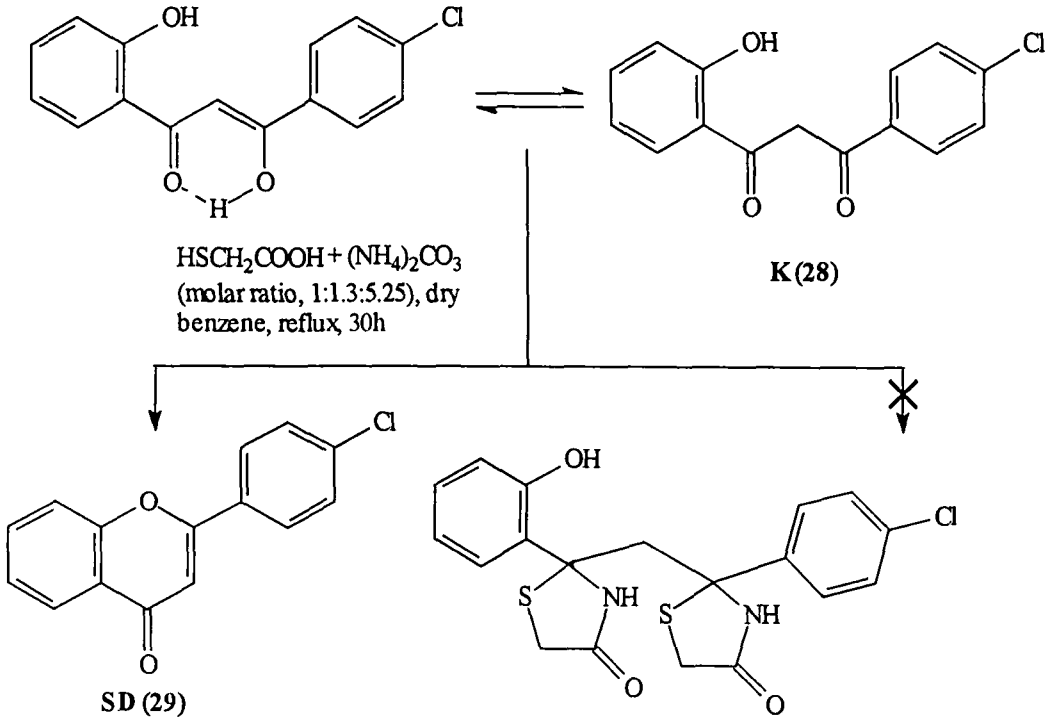
[a]Assignment may be reversed.

On the basis of above facts, the structure of compound **K** was formulated as *2-hydroxy-4'-chlorodibenzoyl methane (28)*.



Synthesis of 4'-chloroflavone SD (29) [from 2-hydroxy-4'-chlorodibenzoyl methane K (28) using thioglycollic acid and ammonium carbonate in dry benzene

A mixture of 2-hydroxy-4'-chlorodibenzoylmethane **K (28)**, thioglycollic acid and ammonium carbonate (molar ratio, 1:1.30 : 5.25) in dry benzene was refluxed for 30 h. The products were purified by column chromatography over silica gel column using pet. ether-diethyl ether as eluent (8:2 v/v) followed by crystallization from benzene-acetone which yielded **SD (29)** as white crystalline needles in 80% yield.



Structure Elucidation of SD (29)

It is a white crystalline solid, m.p. 150 °C and appears grey on exposure to iodine vapours (TLC). The constitution of **SD** has been established by DCI-MS, ^{1}H-NMR and ^{13}C-NMR spectra. The DCI-MS (NH_3 as reagent gas) of **SD (29) (FIG. 64)** showed $[M+H]^+$ peaks at m/z 257/259 (100.0/36.3) confirming its molecular weights 256/258 which corresponds with the molecular formula $[C_{15}H_9O_2Cl]$. The other significant peaks were observed at m/z 228 (3.9), 137 (6.1), 120 (11.5), 92 (16.7). The mode of fragmentation is shown in **CHART-21**.

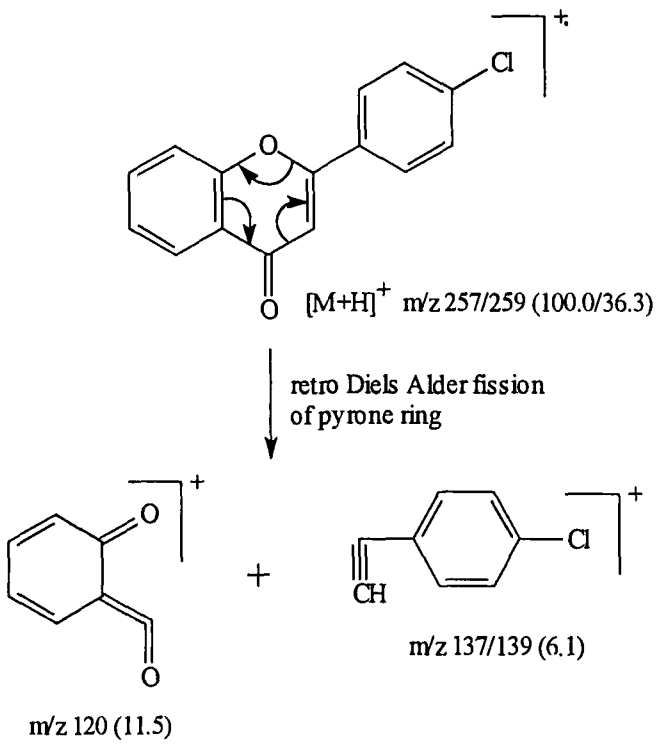
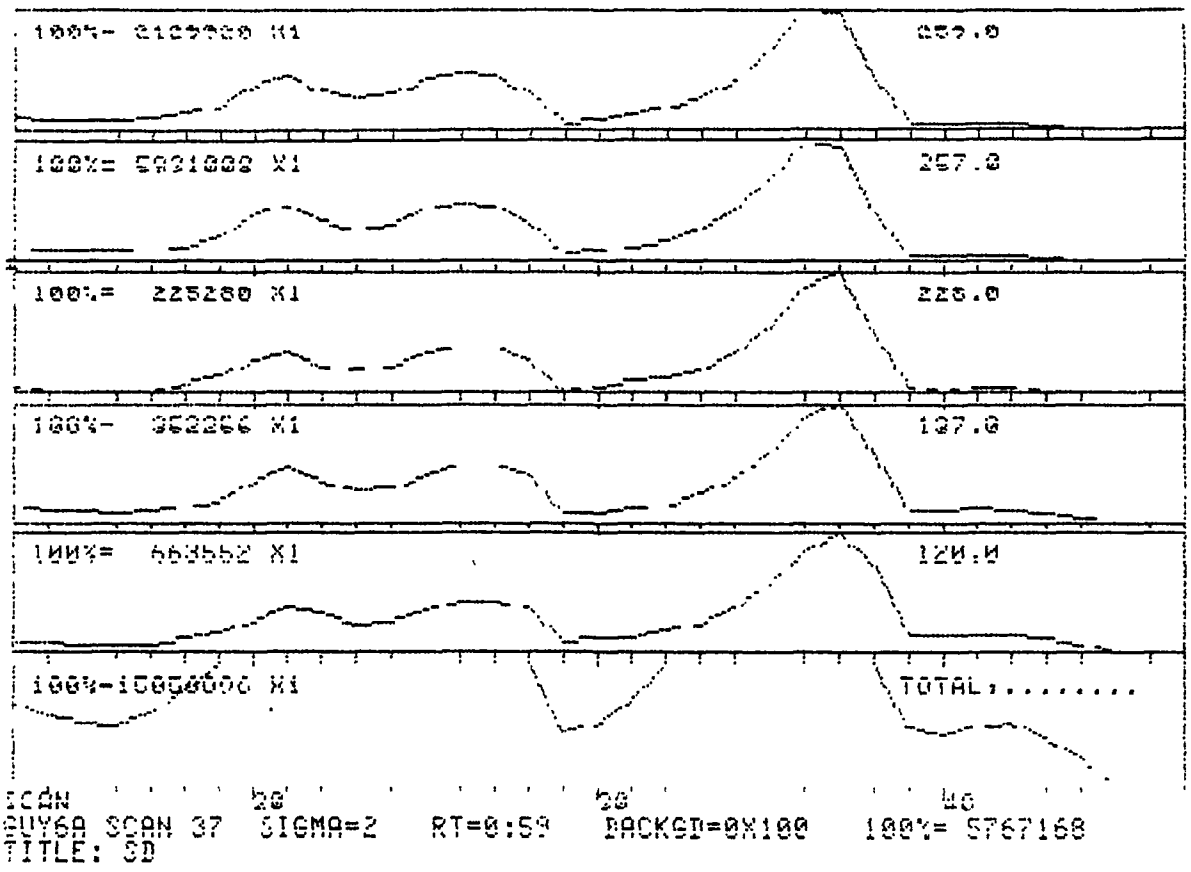
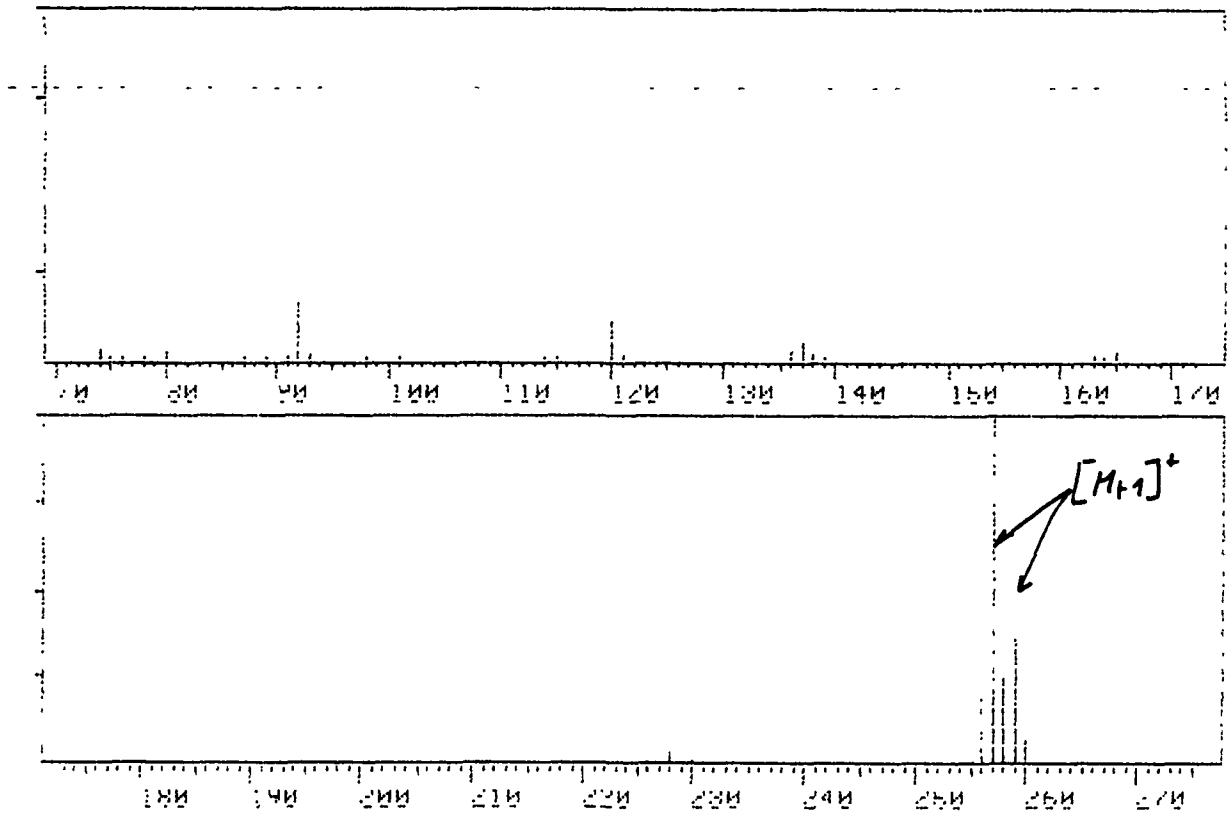


CHART - 22

The ^{1}H-NMR **(FIG. 65)** and ^{13}C-NMR **(FIG. 66)** spectra of **SD** dissolved in acetone-d_6 showed signals as assigned in **TABLE 22**. The assignments of all ^{1}H-NMR and ^{13}C-NMR signals to individual H- and C-atoms have been performed on the basis of their typical chemical shift values, multiplicity and relative integrations. The ^{1}H-NMR spectrum of





92.00	16.7	228.00	3.9	258.00	25.5
120.00	11.5	256.00	19.3	259.00	36.3
137.00	6.1	257.00	100.0	260.00	7.0

FIG. 64

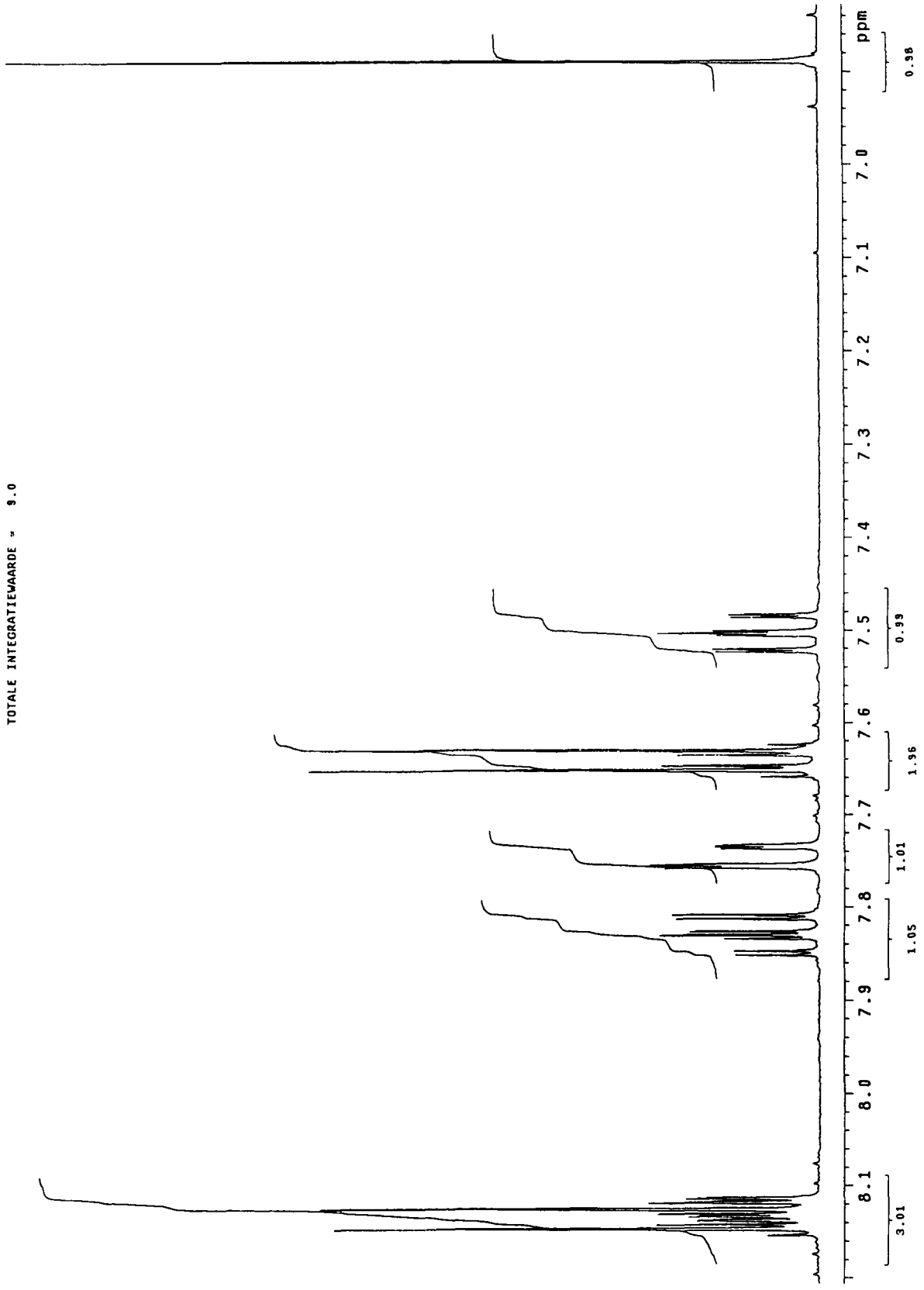

TOTALE INTEGRATIEWAARDE = 9.0
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
ppm
3.01
1.05
1.01
1.96
0.93
0.98

FIG. 65

INDEX	FREQUENCY	PPM	HEIGHT
1	20713.68	206.01	1445.4
2	20693.84	205.81	22.6
3	20674.00	205.61	5.7
4	20635.85	205.23	3.0
5	17877.74	177.80	17.7
6	16367.08	162.78	18.0
7	15800.96	157.15	17.6
8	13882.11	138.06	16.6
9	13565.48	134.92	79.6
10	13240.46	131.68	23.6
11	13087.10	130.16	179.4
12	12965.03	128.94	171.5
13	12694.17	126.25	86.2
14	12671.29	126.02	75.7
15	12556.08	124.88	20.2
16	11992.25	119.27	81.8
17	10892.82	108.33	105.5
18	3055.67	30.39	178.7
19	3036.59	30.20	526.3
20	3016.75	30.00	985.4
21	2997.68	29.81	1254.6
22	2978.61	29.62	1025.3
23	2958.77	29.43	516.7
24	2939.70	29.24	182.1
25	2919.10	29.03	6.1
26	-0.00	-0.00	4.2

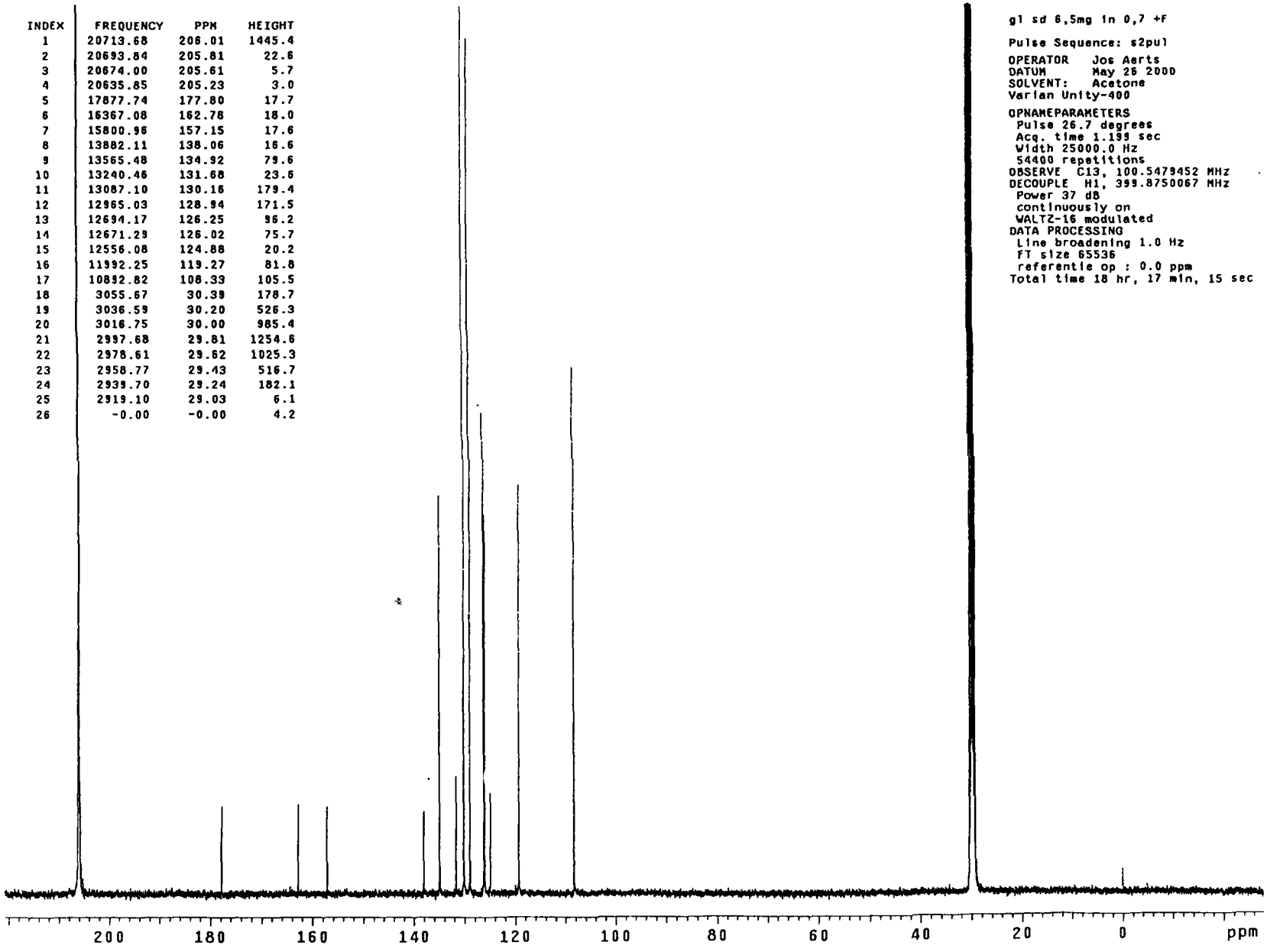


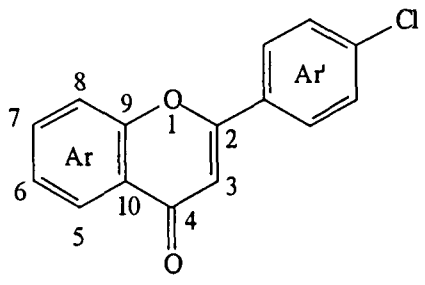
FIG. 66

TABLE - 22 : ^{1}H-NMR and ^{13}C-NMR spectral data of SD(29)

H-nr	δ (ppm)	Inte-gration	multi-plicity	J(Hz)	C-nr	δ (ppm)
3	6.89	1H	s	–	2	162.78
Ar-5	8.13	1H	dd	$J_{5,6}$=9.15, $J_{5,7}$=1.83	3	108.33
Ar-6	7.50	1H	ddd	$J_{5,6}$=9.15, $J_{6,7}$=7.17	4	177.80
				$J_{6,8}$=1.22	Ar-5	126.25
Ar-7	7.84	1H	ddd	$J_{6,7}$=7.17, $J_{7,8}$=8.55	Ar-6	126.02
				$J_{5,7}$=1.83	Ar-7	134.92
Ar-8	7.75	1H	dd	$J_{7,8}$=8.55, $J_{6,8}$=1.22	Ar-8	119.27
Ar'-2,6	8.14	2H	d	$J_{Ar'-2,6}$=8.85	Ar-9	157.15
Ar'-3,5	7.64	2H	d	$J_{Ar'-3,5}$=8.85	Ar-10	124.88
					Ar'-1	131.68
					Ar'-2,6	128.94
					Ar'-3,5	130.16
					Ar'-4	138.06

SD showed two triple doublets at δ7.50 and δ7.84 with coupling constant J=9.15 Hz, J=7.17 Hz, J=1.22 Hz and J=7.17 Hz; J=8.55 Hz, J=1.83 Hz which were assigned to Ar-6 and Ar-7. The two double doublets appeared at δ8.13 and δ7.75 with coupling constant J=9.15 Hz, J=1.83 Hz and J=8.55 Hz, J=1.22 Hz were attributed to Ar-5 and Ar-8. The signal at δ6.89 was assigned to H-3. The other aromatic signals appeared as A_2B_2 system at δ8.14 and δ7.64 as doublets with coupling constant J=8.85 Hz were attributed to H-Ar'-2,6 and H-Ar'-3,5. The ^{13}C-NMR spectrum showed signals as assigned **(TABLE-22)**. The characteristic peak appeared at δ177.80 for carbonyl carbon and the other carbon signals are at δ162.78 (C-2) and δ108.33 (C-3). The ring carbon signals appeared at δ126.25 (C-Ar-5), 126.02(C-Ar-6), 134.92(C-Ar-7), 119.27(C-Ar-8), 157.15 (C-Ar-9), 124.88 (C-Ar-10), 131.68 (C-Ar'-1), 128.94 (C-Ar'-2,6), 130.16 (C-Ar'-3,5) and 138.06 (C-Ar'-4). The ^{13}C-NMR spectral data are thus in agreement with the assigned structure.

On the basis of above evidence, **SD** was characterized as *4'-chloro flavone (29)*.



SD (29)

Experimental

EXPERIMENTAL

2-Hydroxy-4'-chlorodibenzoylmethane K (28) from 2-(4'-chlorobenzoyloxy)acetophenone (27) by Baker-Venkataraman transformation

2-(4'-chlorobenzoyloxy)acetophenone **(27)** was prepared following a reported procedure[43] by condensing *o*-hydroxyacetophenone with *p*-chlorobenzoic acid in equimolar ratio in the presence of $POCl_3$. To the solution of *o*-hydroxyocetophenone (1550 mg, 11.40 mmol) and *p*-chlorobenzoic acid (1778 mg, 11.40 mmol) in pyridine (25 ml) was added $POCl_3$ (2ml) dropwise so as to maintain the temperature of the reaction mixture at 50 °C. The reaction mixture was further stirred for 2 h. The semisolid mass thus obtained was decomposed with ice cold 50% HCl (50 ml) to give yellow solid product which was washed with 0.5% aqueous NaOH (5ml). It was then crystallized from ethanol to give **(27)** as yellow crystalline needles, 2029 mg (65%), m.p. 115 °C, R_f 0.64 (pet. ether - diethyl ether, 8:2 v/v).

Baker-Venkataraman transformation

2-(4'-chlorobenzoyloxy)acetophenone (1350 mg, 4.93 mmol) was dissolved in pyridine (20 ml) and pulverzid KOH (551mg, 9.85 mmol) added to it in several lots with constant stirring. After complete addition, the reaction mixture was stirred for 7.5 h. The resulting yellowish red mass obtained was decomposed with ice-cold 1:1 HCl (50 ml). The yellow solution was extracted with ethyl acetate and the organic phase washed with 10% $NaHCO_3$ solution and with water, dried over anhydrous Na_2SO_4. The product obtained after distilling off the solvent on crystallization from ethanol yielded **K (28)** as yellow crystalline needles, 810 mg (60%), m.p. 122 °C, R_f 0.76 (pet. ether-diethyl ether, 8:2 v/v).

Spectral data of K (28)

^{1}H-NMR (acetone-d_6, 400 MHz) : δ_H 4.91 (2H, s, H-2_{keto}), 7.31 (1H, s, H-2_{enol}), 11.83 (1H, s, enolic OH), 11.88 (1H, s, H-Ar-OH), 7.00-8.15 (4H, brm, H-Ar'), 8.14 (2H, d, J=8.55Hz, H-Ar-2,6), 7.68 (2H, d, J=8.55Hz, H-Ar-3,5).

^{13}C-NMR (acetone-d_6, 100 MHz) : δ_C 50.26 (C-2_{keto}), 94.01 (C-2_{enol}), 196.80 (C-1_{enol})/1_{keto}), 177.43 (C-3_{enol}/3_{keto}), 133.25 (C-Ar'-1), 163.25 (C-Ar'-2), 119.22 (C-Ar'-3), 137.09 (C-Ar'-4), 120.20 (C-Ar'-5), 130.51 (C-Ar'-6), 131.24 (C-Ar-1), 129.92 (C-Ar-2,6), 129.61 (C-Ar-3,5), 139.13 (C-Ar-4).

DCI-MS (NH_3) : m/z 278/277/276/275/274 (6.3/35.4/20.2/100.0/3.9), 141/139 (4.8/14.8), 121 (6.1).

4'-Chloroflavone SD (29)

A mixture of 1,3-diketone **K (28)** (770 mg, 2.81 mmol), thioglycollic acid (336mg, 3.7 mmol) and ammonium carbonate (1416 mg, 14.75 mmol) in dry benzene (20 ml) was refluxed for 30 h with stirring at 80°C on an oil bath. The progress of the reaction was monitored by TLC at every 30 minutes. After the reaction was over, the reaction mixture was concentrated under reduced pressure, extracted with diethyl ether and washed with water until the solution became neutral. The ethereal solution was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The residue left was finally examined by TLC (silica gel 'G' pet. ether diethyl ether, 8:2) which showed only one component, labelled as **SD**. The residue was chromatographed over silica gel column using pet. ether-diethyl ether as an eluent. Elution of the column furnished a solid mass which on crystallization from benzene-acetone afforded **SD (29)** as white crystalline needles, 616 mg (80%), m.p. 150 °C, R_f 0.46 (pet. ether-diethyl ether, 8:2 v/v).

Spectral data of SD (29)

^{1}H-NMR (acetone-d_6, 400 MHz) : δ_H 6.89 (1H, s, H-3), 8.13 (1H, dd, $J_{5,6}$=9.15 Hz, $J_{5,7}$ = 1.83 Hz, H-Ar-5), 7.50 (1H, ddd, $J_{5,6}$=9.15Hz, $J_{6,7}$=7.17 Hz, $J_{6,8}$=1.22 Hz, H-Ar-6), 7.84 (1H, ddd, $J_{6,7}$=7.17Hz, $J_{7,8}$=8.55 Hz, $J_{5,7}$=1.83 Hz, H-Ar-7). 7.75 (1H, dd, $J_{7,8}$=8.55 Hz, $J_{6,8}$=1.22Hz, H-Ar-8), 8.14 (2H, d, $J_{Ar'-2,6}$=8.85 Hz, H-Ar-26), 7.64 (2H, d, $J_{Ar'-3,5}$=8.85 Hz,H-Ar-35).

^{13}C-NMR (acetone-d_6, 100 MHz) : δ_C 162.78 (C-2), 108.33 (C-3), 177.80 (C-4), 126.25 (C-Ar-5), 126.02 (C-Ar-6), 134.92 (C-Ar-7), 119.27 (C-Ar-8), 157.15 (C-Ar-9), 124.88 (C-Ar-10), 131.68 (C-Ar'-1), 128.94 (C-Ar'-2,6), 130.16 (C-Ar'3,5), 138.06 (C-Ar'-4).

DCI-MS (NH_3) : m/z 260/259/258/257/256 (7.0/36.3/25.5/100.0/19.3), 228 (3.9), 137 (6.1), 120 (11.5), 92 (16.7).

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Chapter - 6

Biological Screening

Biological Screening : Study for Anticancer and Antibacterial Activities

(A). ANTICANCER ACTIVITY AGAINST MALIGNANT HUMAN TUMOUR CELLS :

INTRODUCTION

The compounds are evaluated as a single dose primary anticancer assay in 3-cell lines panels consisting of three types of human cancers : Breast (MCF7), Lung (NCI-H460) and CNS(SF-268). In the screening protocol, each cell line is inoculated and preincubated for 24-28 h on a microtiter plate. Test agents are then added at a single concentration and the culture incubated for further 48 h. End-point determinations are made with alamar blue[1]. Results for each test agent are reported as the percent of growth of the treated cells when compared to the untreated control cells. Compounds which reduce the growth of anyone of the cell lines to 32% or less (negative number indicates cell kill) are then passed on for evaluation in the full panel of 60-cell lines over a 5-log dose range[2].

In the full panel of 60-cell lines, 9 types of human cancers, namely, leukemia, lung cancer, colon cancer, central nervous system, melanoma, ovarian, renal, prostate and breast are used. These test agents are added in five 10-fold dilutions and a 48 hours continuous drug exposure protocol is used. Sulphorhodamine B (SRB), a protein-binding dye assay, is used to estimate cell viability or growth. Results are expressed as $\log_{10}$ GI50 which is the drug concentration (M) causing a 50% reduction in the net protein increase in control cells during the drug incubation.

Data Analysis

The calculated Measurement of Effect : Percentage Growth (PG).

The measured effect of the compound on a cell line is currently calculated according to one or the other of the following two expressions.

If (Mean OD_{test} - Mean OD_{tzero}) ≥ 0. then

$PG = 100 \times (\text{Mean } OD_{test} - \text{Mean } OD_{tzero}) / \text{Mean } OD_{tzero}$

Where :

Mean OD_{tzero} = The average optical density measurements of SRB-derived colour just before exposure of cell to the test compound.

Mean OD_{test} = The average optical density measurements of SRB-derived colour after 48 hours exposure of cell to the test compound.

Mean $OD_{ctrl.}$ = The average optical density measurements of SRB-derived colour after 48 hours with no exposure of cell to the test compound.

The results as obtained from experimental data are represented in three ways.

(i) *The Data Sheet :*

The first two columns of the Table describe the subpanel and cell lines involved. The next two columns list the Mean OD_{tzero} and Mean $OC_{ctrl.}$: the next five columns list the Mean OD_{test} for each five different concentrations. Each concentration is expressed as the $\log_{10}$ (molar or μg/ml). The next five columns list the calculated PGs for each concentration. The response parameters G150, TGI, and LC50 are interpolated values representing the concentrations at which the PG is +50.0 and -50.0 respectively.

(ii) *Dose-Response Curves :*

The dose-response curve plot of the data package is created by plotting the PGs against the $\log_{10}$ of the corresponding concentration for every cell line. The cell line curves are grouped by subpanel : horizontal lines are provided at the PG values of + 50.0 and -50. The concentrations corresponding to points where the curves cross these lines are the GI50, TGI and LC50 respectively.

(iii) *The Mean Graphs :*

The mean graphs show mean graphs at each of the principal response parameters : GI50, TGI and LC50. Bars extending to the right representing sensitivity of cell lines to the test agent in excess of the average sensitivity of all tested cell lines. Since the bar scale is logarithmic, a bar 2 units to the right implies the compound achieved the response parameters (eg. GI50) for the cell line at the concentration one-hundredth the mean concentration required over all cell lines, and thus the cell line is usually sensitive to that compound. Bar extending to the left correspondingly imply sensitivity less than the mean.

RESULTS AND DISCUSSION

The compounds [**P(2)**, **E_{1A}(3)**, **ClFD(9)**, **$ClFD_{1C}$(10)**, **SD_5(12)**, **SD_{4A}(14)**, **SD_{1A}(19)**, **SD_{1B}(20)**, **Q(25)**] were evaluated as one dose primary anticancer assay in three cell line panel and the results are depicted in **TABLE 23**. Out of the nine compounds screened, only two compounds, **E_{1A}(3)** and **Q(25)** were found to be active. These compounds were then screened for cytotoxic activity[2] at five different concentrations against 60 cell lines of nine types of human cancers : leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast. A 48 h continuous drug exposure protocol was used and a sulphorhodamine B protein assay was used to estimate cell viability or growth. Results in **TABLE-24** and **TABLE-25** are expressed as $\log_{10}$GI50 which is the drug concentration (M) causing 50% reduction in the net protein increase in control cells during the drug incubation. These compounds showed activity only at higher concentration. Noteworthy results were obtained for the compounds **E_{1A}(3)** in the case of melanoma, colon, renal cancers where the reduction in growth is 52, 80 and 91% respectively **TABLE-26** and for the compound **Q(25)** in the case of melanoma and colon cancers where the reduction in growth is 48 and 83% respectively **(TABLE-27)**.

TABLE-23 : Results of anticancer activity of the compounds against 3-cell lines of human cancers

Test Compounds	Concentration	Percent growth			
		(Lung) NCI-H460	(Breast) MCF7	(CNS) SF-268	Activity
P(2)	$1x10^{-4}M$	62	32	49	Inactive
$E_{1A}(3)$	$1 \times 10^{-4}M$	-11	3	7	Active
ClFD (9)	$1 \times 10^{-4}M$	75	91	74	Inactive
$ClFD_{1C}(10)$	$1 \times 10^{-4}M$	114	81	126	Inactive
SD_{1A} (19)	$1 \times 10^{-4}M$	117	100	121	Inactive
SD_{4A} (14)	$1 \times 10^{-4}M$	119	98	123	Inactive
SD_5 (12)	$1 \times 10^{-4}M$	87	84	91	Inactive
SD_{1B} (20)	$1 \times 10^{-4}M$	82	96	78	Inactive
Q (25)	$1 \times 10^{-4}M$	-42	2	-1	Active

The compound $E_{1A}(3)$ has shown some cytotoxic effect only in renal cancer [SN12C] at the concentration of 1×10^{-5} m of the compound.

The dose response curves of the compound $E_{1A}(3)$ and Q(26) treated with different malignant human tumour cell lines have been deciphered in **FIG. 67** and **FIG. 68**.

The overall anticancer effect of the compounds (3) and (25) on all the human tumour cell lines is illustrated in **FIG. 69** and **FIG. 70** respectively.

Mean graphs of the compound (3) and (25) which facilitate visual scanning of data for potential patterns of selectivity for particular cell lines with respect to a selected response parameters are represented in **FIG. 71** and **FIG. 72** respectively.

TABLE - 24 National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC: 716408 -N / 1	Experiment ID: 0004MD35-17	Test Type: 08	Units: Molar
Report Date: May 22, 2000	Test Date:	QNS:	MC:
COMI: CODE-E1A	Stain Reagent: SRB Dual-Pass	SSPL: 0GVG	

			Log10 Concentration															
	Time		Mean Optical Densities						Percent Growth									
Panel/Cell Line	Zero	Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0		-8.0	-7.0	-6.0	-5.0	-4.0		GI50	TGI	LC50	
Leukemia																		
CCRF-CEM	0.212	0.798	0.789	0.750	0.705	0.408	0.286		99	92	84	33	13		4.71E-06	>1.00E-04	>1.00E-04	
HL-60(TB)	0.602	2.201	2.031	1.911	1.929	1.019	0.413		89	82	83	26	-31		3.80E-06	2.84E-05	>1.00E-04	
K-562	0.210	1.531	1.535	1.567	1.532	0.603	0.280		100	103	100	30	5		5.15E-06	>1.00E-04	>1.00E-04	
MOLT-4	0.238	0.982	0.995	1.033	0.935	0.312	0.226		102	107	94	10	-5		3.32E-06	4.50E-05	>1.00E-04	
RPMI-8226	0.625	1.912	1.941	1.937	1.906	1.000	0.477		102	102	100	29	24		5.05E-06	3.56E-05	>1.00E-04	
SR	0.289	1.255	1.241	1.279	1.230	0.500	0.202		98	102	97	22	-30		4.24E-06	2.63E-05	>1.00E-04	
Non-Small Cell Lung Cancer																		
A549/ATCC	0.219	1.280	1.306	1.309	1.214	0.616	0.400		102	103	94	37	17		5.97E-06	>1.00E-04	>1.00E-04	
EKVX	0.381	0.852	0.835	0.859	0.867	0.660	0.468		96	101	103	59	18		1.69E-05	>1.00E-04	>1.00E-04	
HOP-62	0.520	1.089	1.069	1.096	1.101	0.862	0.491		96	101	102	60	-6		1.42E-05	8.20E-05	>1.00E-04	
HOP-92	0.799	1.280	1.280	1.316	1.289	1.104	0.727		100	107	102	63	-9		1.53E-05	7.50E-05	>1.00E-04	
NCI-H226	0.412	0.879	0.871	0.867	0.846	0.659	0.311		98	97	92	50	-30		9.76E-06	4.22E-05	>1.00E-04	
NCI-H23	0.527	1.300	1.362	1.368	1.320	0.909	0.662		108	109	103	49	17		9.76E-06	>1.00E-04	>1.00E-04	
NCI-H322M	0.262	0.842	0.865	0.856	0.845	0.708	0.470		104	102	100	77	36		4.50E-05	>1.00E-04	>1.00E-04	
NCI-H460	0.295	1.726	1.718	1.689	1.679	0.982	0.309		99	97	97	48	1		9.03E-06	>1.00E-04	>1.00E-04	
NCI-H522	0.609	1.527	1.506	1.594	1.559	0.949	0.623		98	107	101	37	2		6.28E-06	>1.00E-04	>1.00E-04	
Colon Cancer																		
COLO 205	0.206	0.774	0.766	0.774	0.760	0.361	0.041		98	100	97	27	-80		4.75E-06	1.79E-05	5.22E-05	
HCC 2998	0.330	1.130	1.094	1.113	1.114	0.862	0.408		95	98	98	66	10		1.95E-05	>1.00E-04	>1.00E-04	
HCT 116	0.281	2.013	2.082	2.017	1.969	1.132	0.421		104	100	97	49	8		9.59E-06	>1.00E-04	>1.00E-04	
HCT-15	0.304	1.669	1.727	1.776	1.641	1.002	0.543		104	108	98	51	17		1.08E-05	>1.00E-04	>1.00E-04	
HT29	0.196	1.177	1.206	1.158	1.224	0.676	0.262		103	98	105	49	7		9.54E-06	>1.00E-04	>1.00E-04	
KM12	0.489	2.236	2.118	2.221	2.020	1.457	0.713		93	99	88	55	13		1.34E-05	>1.00E-04	>1.00E-04	
SW-620	0.195	1.109	1.124	1.076	1.053	0.735	0.418		102	96	94	59	24		1.83E-05	>1.00E-04	>1.00E-04	
CNS Cancer																		
SF-268	0.530	1.558	1.569	1.609	1.603	1.119	0.811		101	105	104	57	27		1.75E-05	>1.00E-04	>1.00E-04	
SF-295	0.563	1.227	1.218	1.249	1.261	0.743	0.490		99	103	105	27	-13		5.08E-06	4.75E-05	>1.00E-04	
SF-539	0.328	1.029	1.145	0.971	1.098	0.956	0.259		117	92	110	90	-21		2.28E-05	6.44E-05	>1.00E-04	
SNB-19	0.369	1.268	1.232	1.238	1.198	0.959	0.690		96	97	92	66	36		3.32E-05	>1.00E-04	>1.00E-04	
SNB-75	0.565	0.831	0.844	0.840	0.856	0.763	0.640		105	103	110	74	28		3.35E-05	>1.00E-04	>1.00E-04	
U251	0.284	1.170	1.169	1.144	1.085	0.730	0.247		100	97	90	50	13		1.02E-05	6.31E-05	>1.00E-04	
Melanoma																		
LOX IMVI	0.295	1.646	1.668	1.661	1.620	0.923	0.264		102	101	98	46	11		8.54E-06	6.54E-05	>1.00E-04	
MALME-3M	0.604	1.189	1.206	1.242	1.214	1.064	0.561		103	109	104	79	7		2.16E-05	8.26E-05	>1.00E-04	
M14	0.288	1.261	1.232	1.151	1.110	0.791	0.557		97	89	93	52	28		1.18E-05	>1.00E-04	>1.00E-04	
SK-MEL-2	0.411	0.959	0.998	0.973	0.943	0.804	0.393		107	103	97	72	4		1.93E-05	8.76E-05	>1.00E-04	
SK-MEL-28	0.338	0.345	0.834	0.834	0.817	0.677	0.542		98	98	94	67	40		4.29E-05	>1.00E-04	>1.00E-04	
SK-MEL-5	0.450	1.821	1.815	1.825	1.828	1.292	0.215		100	100	100	61	52		1.76E-05	3.47E-05	9.54E-05	
UACC-257	0.689	1.604	1.589	1.560	1.548	1.324	0.722		98	95	94	58	1		1.45E-05	>1.00E-04	>1.00E-04	
UACC-62	0.503	1.594	1.582	1.542	1.497	1.125	0.432		99	95	91	57	14		1.75E-05	6.31E-05	>1.00E-04	
Ovarian Cancer																		
IGROV1	0.356	1.420	1.425	1.434	1.432	1.061	0.652		100	101	101	66	28		2.64E-05	>1.00E-04	>1.00E-04	
OVCAR-3	0.579	2.164	2.197	2.189	2.163	1.796	0.424		106	104	100	37	27		6.21E-06	3.80E-05	>1.00E-04	
OVCAR-4	0.487	2.133	2.149	2.142	2.113	1.750	0.552		102	101	97	41	10		6.82E-06	>1.00E-04	>1.00E-04	
OVCAR-5	0.653	2.123	2.167	2.118	2.125	2.094	0.893		109	99	100	94	51		>1.00E-04	>1.00E-04	>1.00E-04	
OVCAR-8	0.189	0.943	0.926	0.945	0.915	0.616	0.317		98	100	97	57	17		1.46E-05	>1.00E-04	>1.00E-04	
SK-OV-3	0.524	0.938	0.940	0.955	0.943	0.658	0.664		100	104	101	81	34		4.50E-05	>1.00E-04	>1.00E-04	
Renal Cancer																		
786-0	0.211	1.058	1.137	0.894	1.092	0.628	0.197		109	81	104	49	9		9.67E-06	7.12E-05	>1.00E-04	
A498	0.962	1.370	1.383	1.379	1.372	1.189	0.688		103	102	100	56	-29		1.16E-05	4.58E-05	>1.00E-04	
ACHN	0.443	1.387	1.429	1.399	1.375	0.941	0.431		104	101	99	53	-3		1.12E-05	8.94E-05	>1.00E-04	
CAKI-1	0.665	2.483	2.500	2.560	2.479	1.833	0.918		101	104	100	64	14		1.92E-05	>1.00E-04	>1.00E-04	
RXF-393	0.647	1.048	1.026	1.053	1.023	0.705	0.360		97	101	94	14	-44		3.56E-06	1.76E-05	>1.00E-04	
SN12C	0.447	1.245	1.116	1.183	1.160	0.799	0.040		86	95	92	53	91		2.16E-06	5.42E-06	1.95E-05	
TK-10	0.737	1.380	1.390	1.349	1.404	1.315	0.954		104	95	104	90	74		5.12E-05	>1.00E-04	>1.00E-04	
UO-31	0.280	1.013	1.037	1.005	1.002	0.833	0.365		103	99	98	75	12		2.51E-05	>1.00E-04	>1.00E-04	
Prostate Cancer																		
PC-3	0.287	0.719	0.758	0.701	0.704	0.404	0.270		109	96	96	27	6		4.69E-06	6.55E-05	>1.00E-04	
DU-145	0.271	0.929	0.924	0.945	0.892	0.719	0.518		99	102	94	68	38		3.91E-05	>1.00E-04	>1.00E-04	
Breast Cancer																		
MCF7	0.187	0.792	0.819	0.764	0.745	0.334	0.125		104	95	92	24	-33		4.18E-06	2.64E-05	>1.00E-04	
NCI/ADR-RES	0.485	1.208	1.218	1.235	1.165	0.816	0.643		101	104	94	46	27		8.17E-06	>1.00E-04	>1.00E-04	
HS 578T	0.760	1.366	1.364	1.427	1.367	1.192	0.971		100	110	103	71	35		3.82E-05	>1.00E-04	>1.00E-04	
MDA-MB-435	0.395	1.632	1.657	1.625	1.617	1.092	0.556		102	99	99	56	13		1.40E-05	>1.00E-04	>1.00E-04	
MDA-N	0.240	1.552	1.456	1.381	1.408	0.845	0.328		93	87	89	46	7		8.12E-06	>1.00E-04	>1.00E-04	
BT-549	0.671	1.454	1.495	1.523	1.462	1.409	0.912		105	109	101	94	31		4.97E-05	>1.00E-04	>1.00E-04	
T-47D	0.650	1.102	1.117	1.124	1.039	0.760	0.706		102	105	86	29	12		4.28E-06	>1.00E-04	>1.00E-04	

TABLE - 25 National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC: 716407 -M I	Experiment ID: 0004MD35-1b	Test Type: 08	Units: Molar
Report Date: May 22, 2000	Test Date:	QNS:	MC:
COMI: CODE-Q	Stain Reagent: SRB Dual-Pass	SSPL: 0GVG	

Panel/Cell Line	Time Zero	Ctrl	Mean Optical Densities: Log10 Concentration -8 0	-7 0	-6 0	-5 0	4 0	Percent Growth: -8 0	-7 0	-6 0	-5 0	-4 0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0 212	0 863	0 827	0 831	0 845	0 847	0 301	94	95	97	98	14	3 68E-05	>1 00E-04	>1 00E-04
HL-60(TB)	0 604	2 294	2 350	2 305	2 242	2 259	0 464	103	101	97	98	-23	2 49E-05	6 46E-05	>1 00E-04
K-562	0 210	1 571	1 524	1 579	1 551	1 517	0 289	97	101	99	96	6	3 24E 05	>1 00E-04	>1 00E-04
MOLT-4	0 238	1 048	1 034	1 007	1 068	1 034	0 302	98	95	102	98	8	3 42E-05	>1 00E-04	>1 00E-04
RPMI-8226	0 625	1 973	1 967	2 010	2 040	1 999	0 508	100	103	105	102	-19	2 69E-05	7 00E-05	>1 00E-04
SR	0 289	1 252	1 212	1 236	1 299	1 259	0 244	96	98	105	101	-16	2 73E-05	7 35E-05	>1 00E-04
Non-Small Cell Lung Cancer															
A549/ATCC	0 219	1 270	1 341	1 393	1 303	1 325	0 320	107	112	103	105	10	3 78E-05	>1 00E-04	>1 00E-04
EKVX	0 381	0 722	0 738	0 782	0 750	0 764	0 319	105	118	108	112	-16	3 0?E-05	7 47E-05	>1 00E-04
HOP-62	0 520	1 151	1 112	1 187	1 136	1 279	0 495	94	106	98	120	5	3 64E 05	9 14E 05	>1 00E-04
HOP 92	0 799	1 261	1 270	1 265	1 235	1 283	0 600	102	101	94	105	-25	2 64E 05	6 42E-05	>1 00E 04
NCI H226	0 442	0 859	0 838	0 864	0 869	0 863	0 437	95	101	102	101	1	3 16E 05	9 75E 05	>1 00E 04
NCI-H23	0 527	1 327	1 358	1 364	1 330	1 329	0 496	104	105	100	100	-6	2 97E 05	8 78E-05	>1 00E-04
NCI-H322M	0 262	0 735	0 726	0 742	0 754	0 715	0 330	98	101	104	96	14	3 66E 05	>1 00E-04	>1 00E 04
NCI-H460	0 295	1 736	1 731	1 749	1 748	1 628	0 349	100	101	101	93	4	3 01E 05	>1 00E-04	>1 00E-04
NCI-H522	0 609	1 308	1 292	1 213	1 314	1 277	0 498	98	86	101	96	-18	2 51E-05	6 91E-05	>1 00E 04
Colon Cancer															
COLO 205	0 206	0 780	0 777	0 811	0 769	0 771	0 034	99	105	98	98	-83	1 85E-05	3 48E-05	6 54E-05
HCC-2998	0 330	1 140	1 117	1 113	1 106	1 157	0 516	97	97	96	102	23	4 55E-05	>1 00E-04	>1 00E-04
HCT-116	0 281	2 069	2 153	2 063	2 105	2 049	0 287	105	100	102	99	0	3 13E-05	>1 00E-04	>1 00E-04
HCT-15	0 304	1 688	1 680	1 702	1 688	1 693	0 363	99	101	100	100	4	3 34E-05	>1 00E-04	>1 00E-04
HT29	0 196	1 181	1 123	1 166	1 145	1 188	0 283	94	98	96	101	9	3 56E-05	>1 00E-04	>1 00E-04
KM12	0 489	2 139	2 039	2 050	2 156	1 991	0 604	94	95	101	91	7	3 08E-05	>1 00E-04	>1 00E-04
SW-620	0 195	1 157	1 183	1 162	1 118	1 115	0 396	103	100	96	96	21	4 07E-05	>1 00E-04	>1 00E-04
CNS Cancer															
SF-268	0 530	1 461	1 457	1 446	1 435	1 435	0 664	99	98	97	97	14	3 71E 05	>1 00E-04	>1 00E-04
SF-295	0 563	1 415	1 370	1 411	1 446	1 514	0 540	95	100	104	112	-4	3 41E-05	9 20E-05	>1 00E-04
SF-539	0 328	1 256	1 013	1 013	1 074	1 010	0 349	74	74	80	73	2	2 14E-05	>1 00E-04	>1 00E 04
SNB-19	0 369	1 277	1 268	1 280	1 258	1 301	0 571	99	100	98	103	22	4 52E-05	>1 00E-04	>1 00E 04
SNB-75	0 565	0 827	0 846	0 845	0 845	0 834	0 510	107	107	107	103	-10	2 94E-05	8 18E 05	>1 00E-04
U251	0 282	1 231	1 217	1 276	1 242	1 285	0 403	98	105	101	106	13	3 97E 05	>1 00E-04	>1 00E 04
Melanoma															
LOX IMVI	0 295	1 652	1 650	1 685	1 644	1 656	0 258	100	102	99	100	-13	2 79E 05	7 72E-05	>1 00E 04
MALME-3M	0 604	1 181	1 190	1 165	1 111	1 131	0 542	102	97	88	91	10	2 55E 05	7 91E 05	>1 00E 04
M14	0 288	1 320	1 365	1 311	1 334	1 339	0 404	104	99	101	102	11	3 73E 05	>1 00E 04	>1 00E 04
SK-MEL-2	0 411	1 053	1 075	1 071	1 080	1 118	0 215	103	103	104	110	-48	2 40E 05	4 98E-05	>1 00E 04
SK-MEL-28	0 338	0 904	0 883	0 937	0 917	0 890	0 513	96	106	102	98	31	5 17E 05	>1 00E 04	>1 00E 04
SK-MEL-5	0 450	1 851	1 824	1 884	1 865	1 954	0 422	98	102	101	107	6	3 20E 05	8 81E-05	>1 00E 04
UACC-257	0 689	1 614	1 583	1 583	1 585	1 553	0 695	97	97	97	93	1	2 94E 05	>1 00E 04	>1 00E 04
UACC-62	0 503	1 614	1 594	1 588	1 583	1 517	0 564	98	98	97	91	5	3 03E 05	>1 00E 04	>1 00E 04
Ovarian Cancer															
IGROV1	0 356	1 384	1 386	1 366	1 342	1 387	0 454	100	98	96	100	9	3 58E 05	>1 00E 04	>1 00E 04
OVCAR-3	0 579	1 287	1 334	1 310	1 366	1 416	0 513	107	103	111	118	11	3 36E 05	8 16E 05	>1 00E 04
OVCAR-4	0 487	1 105	1 121	1 095	1 070	1 054	0 534	103	98	94	92	8	3 13E 05	>1 00E 04	>1 00E 04
OVCAR 5	0 653	0 978	0 956	0 977	0 984	0 969	0 487	93	100	102	97	25	2 43E 05	6 20E 05	>1 00E 04
OVCAR-8	0 189	0 911	0 921	0 924	0 910	0 925	0 263	101	102	100	102	10	3 68E 05	>1 00E 04	>1 00E 04
SK OV-3	0 524	1 008	0 981	1 000	1 011	1 104	0 497	94	99	101	120	5	3 61E 05	9 08E 05	>1 00E 04
Renal Cancer															
786 0	0 211	1 147	1 177	1 130	1 016	1 113	0 299	103	98	86	96	9	3 41E 05	>1 00E 04	>1 00E 04
A498	0 962	1 401	1 399	1 400	1 405	1 392	0 782	99	100	101	98	19	2 57E 05	6 91E 05	>1 00E 04
ACHN	0 443	1 423	1 398	1 418	1 396	1 397	0 390	97	99	97	97	12	2 71E 05	7 76E 05	>1 00E 04
CAKI-1	0 665	2 551	2 364	2 393	2 405	2 281	0 765	90	92	92	86	5	2 78E 05	>1 00E-04	>1 00E 04
RXF 393	0 647	1 032	1 039	1 037	1 029	1 019	0 508	102	101	99	97	-21	2 48E-05	6 58E-05	>1 00E-04
SN12C	0 447	1 350	1 223	1 175	1 150	1 187	0 468	86	81	78	82	2	2 52E 05	>1 00F-04	>1 00E-04
TK-10	0 737	1 393	1 409	1 273	1 459	1 407	0 818	102	82	110	102	12	3 81E-05	>1 00E-04	>1 00E-04
UO-31	0 280	1 106	1 176	1 066	1 058	1 135	0 291	108	95	94	103	1	3 34E-05	>1 00E 04	>1 00E-04
Prostate Cancer															
PC-3	0 287	0 790	0 821	0 807	0 828	0 820	0 302	106	103	107	106	3	3 49E-05	>1 00E-04	>1 00E-04
DU-145	0 271	0 907	0 932	0 912	0 960	0 952	0 396	104	101	108	107	20	4 49E-05	>1 00E-04	>1 00E-04
Breast Cancer															
MCF7	0 187	0 824	0 815	0 802	0 817	0 805	0 175	99	97	99	97	-7	2 84E-05	8 62E-05	>1 00E-04
NCI/ADR-RES	0 485	1 201	1 202	1 211	1 253	1 258	0 474	100	101	107	108	-2	3 35E-05	9 52E-05	>1 00E-04
HS 578T	0 760	1 244	1 228	1 258	1 190	1 261	0 881	97	103	89	104	25	4 81E-05	>1 00E-04	>1 00E-04
MDA-MB-435	0 395	1 556	1 545	1 487	1 506	1 459	0 381	99	94	96	92	-4	2 73E-05	9 15E-05	>1 00E-04
MDA-N	0 240	1 482	1 463	1 436	1 347	1 340	0 307	98	96	89	89	5	2 91E-05	>1 00E-04	>1 00E-04
BT-549	0 671	1 451	1 500	1 472	1 473	1 566	0 896	106	103	103	115	29	5 66E-05	>1 00E-04	>1 00E-04
T-47D	0 650	1 107	1 131	1 117	1 153	1 149	0 610	105	102	110	109	-6	3 26E 05	8 84E-05	>1 00E-04

TABLE-26 : Anticancer Activity of E_{1A} againt 60 Cell Lines

Type of cancer	Cell line	$log_{10}GI50$	Retardation of growth (%)	Concentration (M)
Leukemia	CCRF-CEM	-5 33	-	-
	HL-60(TB)	-5 42	31	1 0x10 ^{4}
	K-562	-5 29	-	-
	MOLT-4	-5 48	5	1 0x10 ^{4}
	RPMI-8226	-5 30	24	1 0x10 ^{4}
	SR	-5 37	30	1 0x10 ^{4}
Non-small cell	A549/ATCC	-5 22	-	-
Lung cancer	EKVX	-4 77	-	-
	HOP-62	-4 85	6	1 0x10 ^{4}
	HOP-92	-4 82	9	1 0x10 ^{4}
	NCI-H226	-5 01	30	1 0x10 ^{4}
	NCI-H23	-5 01	-	-
	NCI-H322M	-4 35	-	-
	NCI-H460	-5 04	-	-
	NCI-H522	-5 20	-	-
Colon cancer	COLO 205	-5 32	80	1 0x10 ^{4}
	HCC-2998	-4 71	-	-
	HCT-116	-5 02	-	-
	HCT-15	-4 97	-	-
	HT29	-5 02	-	
	KM12	-4 87	-	-
	SW-620	-4 74	-	-
CNS cancer	SF-268	-4 76	-	-
	SF-295	-5 29	13	1 0x10 ^{4}
	SF-539	-4 64	21	1 0x10 ^{4}
	SNB-19	-4 48	-	-
	SNB-75	-4 47	-	-
	U251	-4 99	13	1 0x10 ^{4}
Melanoma	LOX IMVI	-5 07	11	1 0x10 ^{4}
	MALME-3M	-4 67	7	1 0x10 ^{4}
	M14	-4 93	-	-
	SK-MEL-2	-4 71	4	1 0x10 ^{4}
	SK-MEL-28	-4 37	-	-
	SK-MEL-5	-4 90	52	1 0x10 ^{4}
	UACC-257	-4 85	-	-
	UACC-62	-4 90	14	1 0x10 ^{4}
Ovarian cancer	IGROVI	-4 58	-	-
	OVCAR-3	-5 21	27	1 0x10 ^{4}
	OVCAR-4	-5 17	-	-
	OVCAR-5	> -4 00	-	-
	OVCAR-8	-4 84	-	-
	SK-OV-3	-4 35	-	-
Renal cancer	786-0	-5 01	9	1 0x10 ^{4}
	A498	-4 94	29	1 0x10 ^{4}
	ACHN	-4 95	3	1 0x10 ^{4}
	CAKI-1	-4 72	-	-
	RXF-393	-5 42	44	1 0x10 ^{4}
	SN12C	-5 67	33,91	1 0x10 ^{5},1 0x10 ^{4}
	TK-10	-4 29	-	-
	UO-31	-4 60	-	-
Prostate cancer	PC-3	-5 33	6	1 0x10 ^{4}
	DU-145	-4 41	-	-
Breast cancer	MCF7	-5 38	33	1 0x10 ^{4}
	NCI/ADR-RES	-5 09	-	-
	HS578T	-4 42	-	-
	MDA-MB-435	-4 85	-	-
	MDA-N	-5 09	-	-
	BT-549	-4 30	-	-
	T-47D	-5 37	-	-

TABLE-27 : Anticancer of Q(25) against 60 cell line

Type of cancer	Cell line	Retardation of growth (%)	$log_{10}GI50$	Concentration (M)
Leukemia	CCRF-CEM	-4 43	-	1 0x10 ^{4}
	HL-60(TB)	-4 60	23	1 0x10^{-4}
	K-562	-4 49	-	1 0x10^{-4}
	MOLT-4	-4 47	-	1 0x10 ^{4}
	RPMI-8226	-4 57	19	1 0x10^{-4}
	SR	-4 56	16	1 0x10^{-4}
Non-small cell	A549/ATCC	-4 42	-	1 0x10^{-4}
Lung cancer	EKVX	-4 52	16	1 0x10 ^{4}
	HOP-62	-4 44	5	1 0x10 ^{4}
	HOP-92	-4 58	25	1 0x10^{-4}
	NCI-H226	-4 50	1	1 0x10 ^{4}
	NCI-H23	-4 53	6	1 0x10^{-4}
	NCI-H322M	-4 44	-	1 0x10^{-4}
	NCI-H460	-4 52	-	1 0x10 ^{4}
	NCI-H522	-4 60	18	1 0x10 ^{4}
Colon cancer	COLO 205	-4 73	83	1 0x10^{-4}
	HCC-2998	-4 34	-	1 0x10 ^{4}
	HCT-116	-4 50	-	1 0x10^{-4}
	HCT-15	-4 48	-	1 0x10 ^{4}
	HT29	-4 45	-	1 0x10 ^{4}
	KM12	-4 51	-	1 0x10^{-4}
	SW-620	-4.39	-	1 0x10^{-4}
CNS cancer	SF-268	-4.43	-	1 0x10^{-4}
	SF-295	-4 47	4	1 0x10 ^{4}
	SF-539	-4 67	-	1 0x10^{-4}
	SNB-19	-4 34	-	1 0x10 ^{4}
	SNB-75	-4 53	10	1 0x10 ^{4}
	U251	-4 40	-	1 0x10^{-4}
Melanoma	LOX IMVI	-4 55	13	1 0x10 ^{4}
	MALME-3M	-4 59	10	1 0x10 ^{4}
	M14	-4 43	-	1 0x10 ^{4}
	SK-MEL-2	-4 62	48	1 0x10^{-4}
	SK-MEL-28	-4 29	-	1 0x10^{-4}
	SK-MEL-5	-4 49	6	1 0x10^{-4}
	UACC-257	-4 53	-	1 0x10 ^{4}
	UACC-62	-4 52	-	1 0x10 ^{4}
Ovarian cancer	IGROVI	-4 45	-	1 0x10 ^{4}
	OVCAR-3	-4 47	11	1 0x10 ^{4}
	OVCAR-4	-4.50	-	1 0x10^{-4}
	OVCAR-5	-4 61	25	1 0x10^{-4}
	OVCAR-8	-4 43	-	1 0x10 ^{4}
	SK-OV-3	-4 44	5	1 0x10 ^{4}
Renal cancer	786-O	-4 47	-	1 0x10 ^{4}
	A498	-4 59	19	1 0x10 ^{4}
	ACHN	-4 57	12	1 0x10^{-4}
	CAKI-I	-4 56	-	1 0x10 ^{4}
	RXF-393	-4 61	21	1 0x10 ^{4}
	SN12C	-4 60	-	1 0x10^{-4}
	TK-10	-4 42	-	1 0x10 ^{4}
	UO-31	-4 48	-	1 0x10 ^{4}
Prostate cancer	PC-3	-4 46	-	1 0x10 ^{4}
	DU-145	-4 35	-	1 0x10^{-4}
Breast cancer	MCF7	-4 55	7	1 0x10^{-4}
	NCI/ADR-RES	-4 47	2	1 0x10^{-4}
	HS578T	-4 32	-	1 0x10^{-4}
	MDA-MB-435	-4 56	4	1 0x10^{-4}
	MDA-N	-4 54	-	1 0x10^{-4}
	BT-549	-4 25	-	1 0x10^{-4}
	T-47D	-4 49	6	1 0x10^{-4}

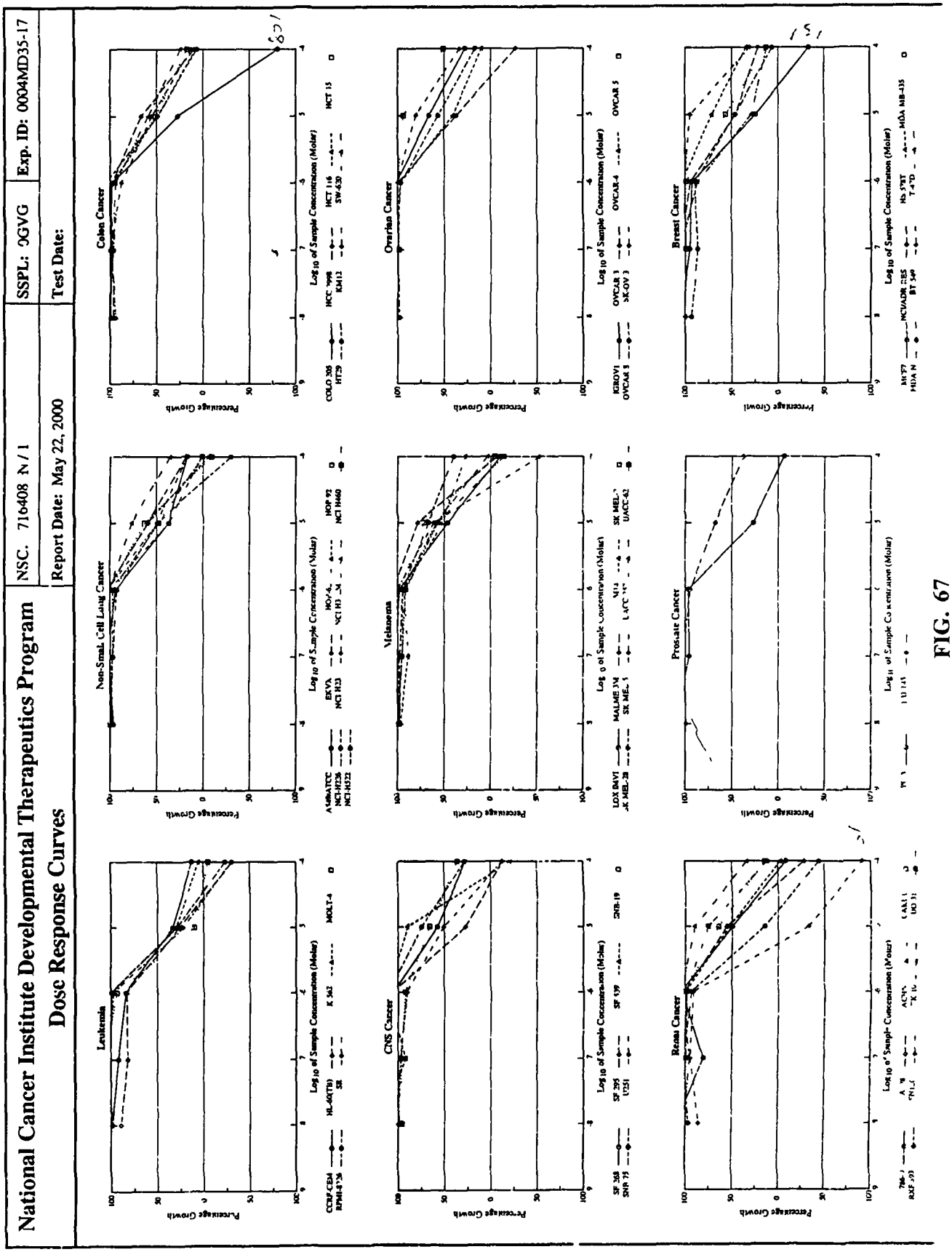
National Cancer Institute Developmental Therapeutics Program
Dose Response Curves
NSC: 716408 N / 1
SSPL: 9GVG
Exp. ID: 0004MD35-17
Report Date: May 22, 2000
Test Date:
Leukemia
Non-Small Cell Lung Cancer
Colon Cancer
CNS Cancer
Melanoma
Ovarian Cancer
Prostate Cancer
Breast Cancer
Renal Cancer
Percentage Growth
Log 10 of Sample Concentration (Molar)

FIG. 67

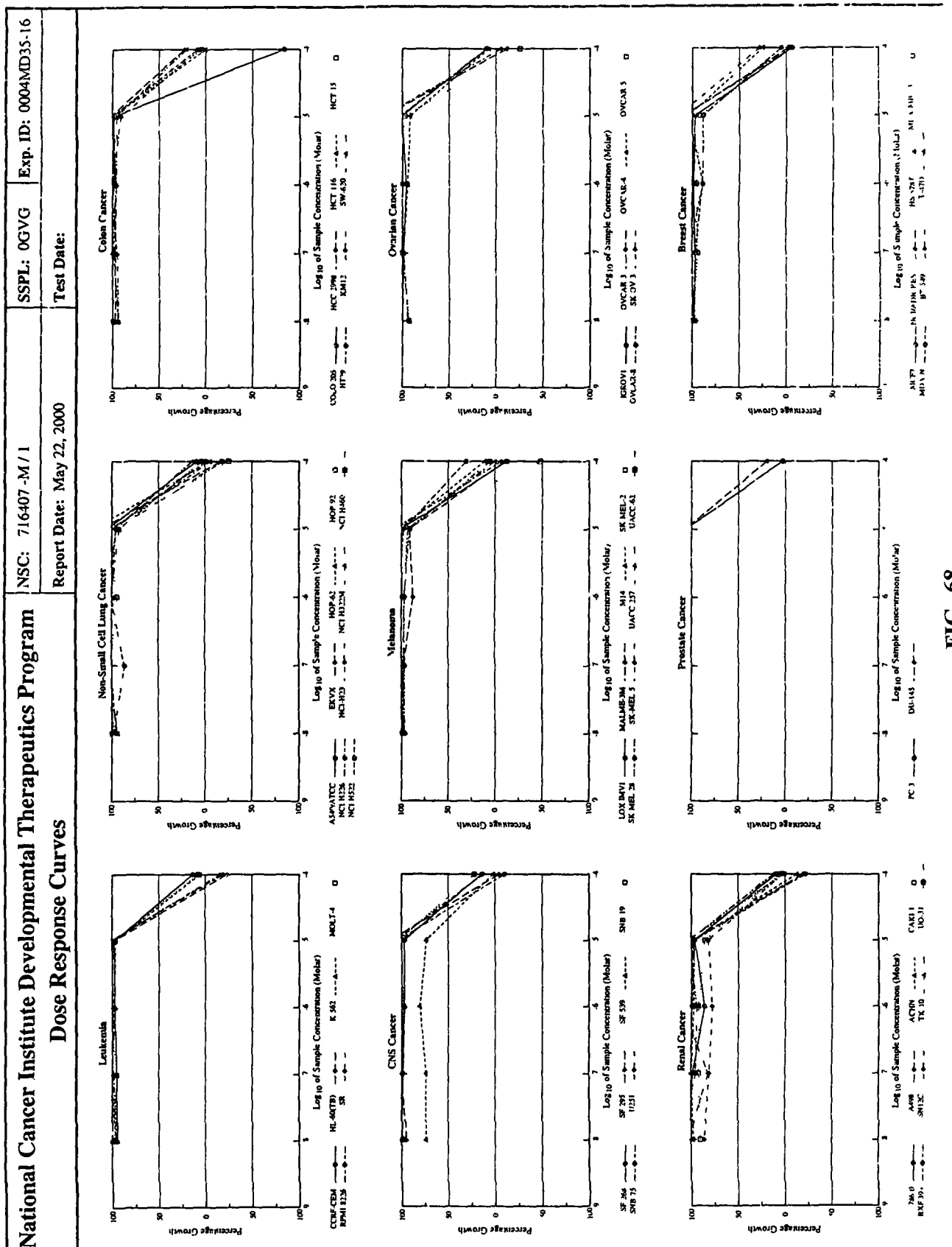
National Cancer Institute Developmental Therapeutics Program
Dose Response Curves
NSC: 716407-M/1
Report Date: May 22, 2000
SSPL: 0GVG
Exp. ID: 0004MD35-16
Test Date:
Leukemia
Non-Small Cell Lung Cancer
Colon Cancer
CNS Cancer
Melanoma
Ovarian Cancer
Renal Cancer
Prostate Cancer
Breast Cancer
Percentage Growth
Log 10 of Sample Concentration (Molar)

FIG. 68

National Cancer Institute Developmental Therapeutics Program Dose Response Curves	NSC: 716408 -N / 1	SSPL: 0GVG	Exp. ID: 0004MD35-17
	Report Date: May 22, 2000	Test Date:	

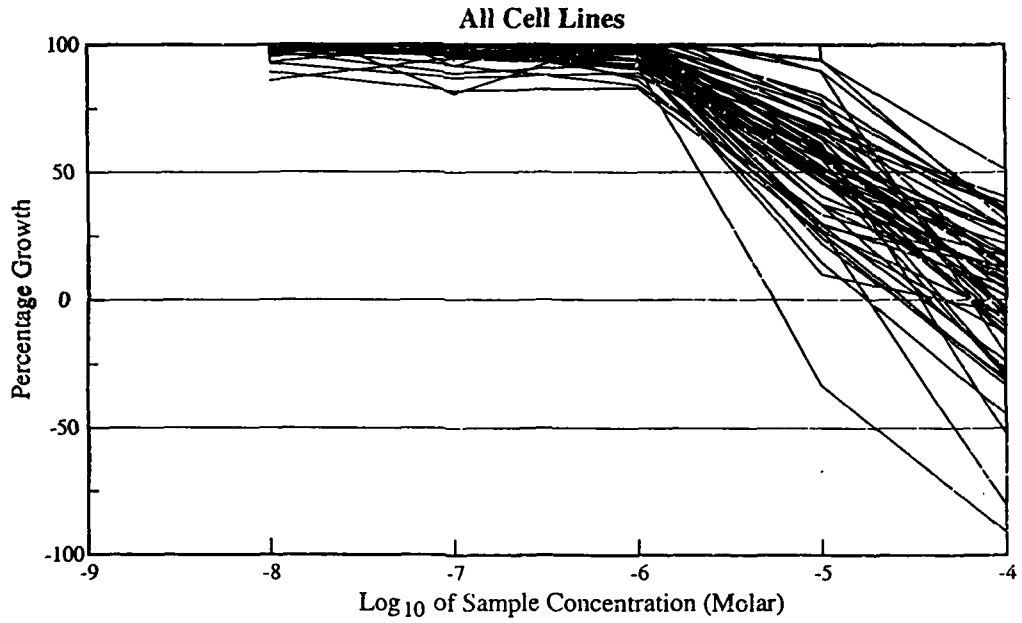

FIG. 69

National Cancer Institute Developmental Therapeutics Program Dose Response Curves	NSC: 716407 -M / 1	SSPL: 0GVG	Exp. ID: 0004MD35-16
	Report Date: May 22, 2000	Test Date:	

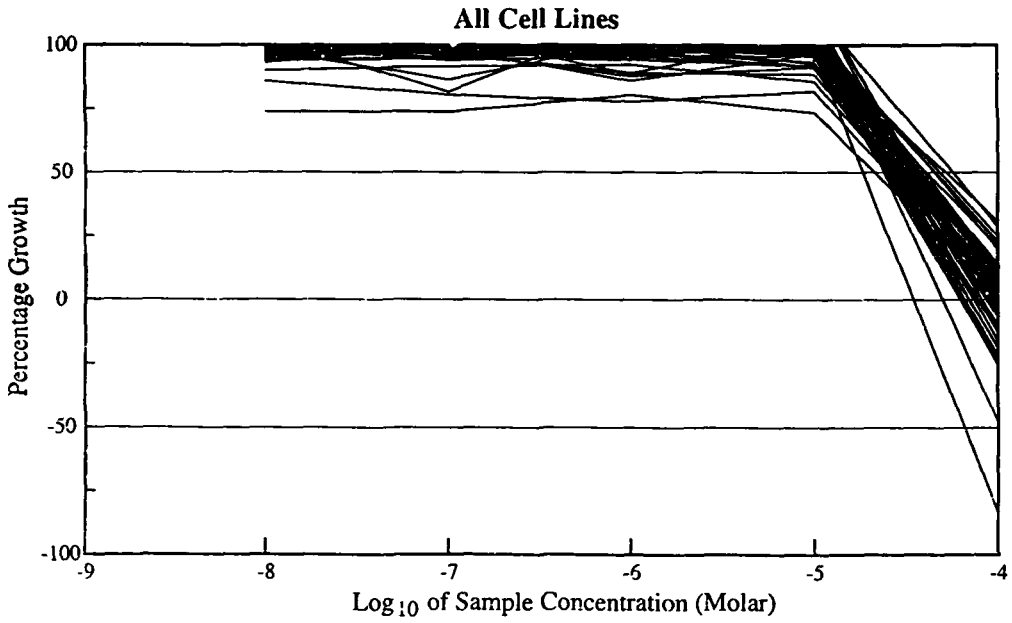

FIG. 70

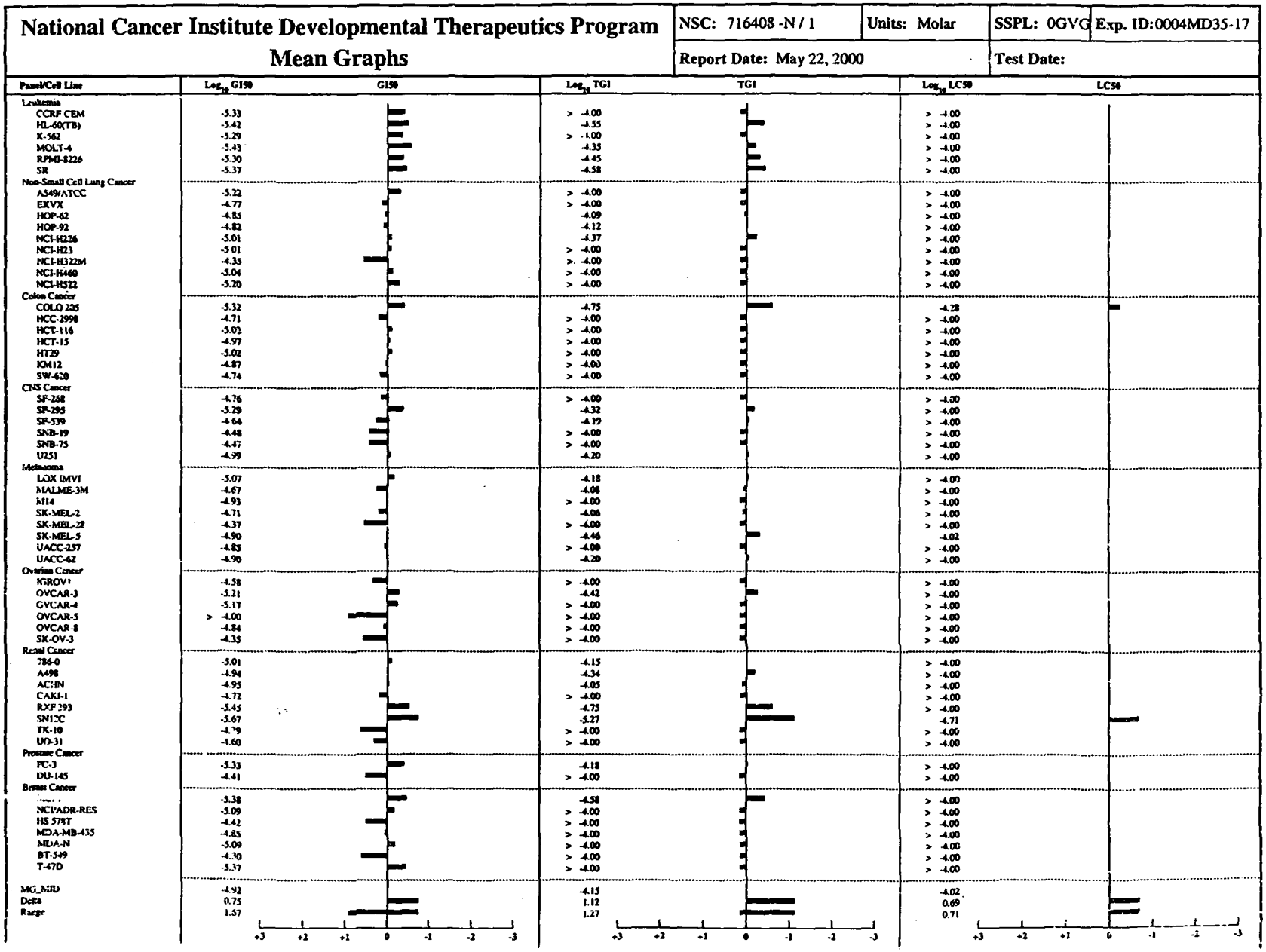
National Cancer Institute Developmental Therapeutics Program
Mean Graphs
NSC: 716408 -N / 1
Units: Molar
SSPL: 0GVG
Exp. ID:0004MD35-17
Report Date: May 22, 2000
Test Date:
Panel/Cell Line
Log10 GI50
GI50
Log10 TGI
TGI
Log10 LC50
LC50
Leukemia
CCRF CEM -5.33 > -4.00 > -4.00
HL-60(TB) -5.42 -4.55 > -4.00
K-562 -5.29 > -4.00 > -4.00
MOLT-4 -5.43 -4.35 > -4.00
RPMI-8226 -5.30 -4.45 > -4.00
SR -5.37 -4.58 > -4.00
Non-Small Cell Lung Cancer
A549/ATCC -5.22 > -4.00 > -4.00
EKVX -4.77 > -4.00 > -4.00
HOP-62 -4.85 -4.09 > -4.00
HOP-92 -4.82 -4.12 > -4.00
NCI-H226 -5.01 -4.37 > -4.00
NCI-H23 -5.01 > -4.00 > -4.00
NCI-H322M -4.35 > -4.00 > -4.00
NCI-H460 -5.04 > -4.00 > -4.00
NCI-H522 -5.20 > -4.00 > -4.00
Colon Cancer
COLO 205 -5.32 -4.75 -4.28
HCC-2998 -4.71 > -4.00 > -4.00
HCT-116 -5.02 > -4.00 > -4.00
HCT-15 -4.97 > -4.00 > -4.00
HT29 -5.02 > -4.00 > -4.00
KM12 -4.87 > -4.00 > -4.00
SW-620 -4.74 > -4.00 > -4.00
CNS Cancer
SF-268 -4.76 > -4.00 > -4.00
SF-295 -5.29 -4.32 > -4.00
SF-539 -4.64 -4.19 > -4.00
SNB-19 -4.48 > -4.00 > -4.00
SNB-75 -4.47 > -4.00 > -4.00
U251 -4.99 -4.20 > -4.00
Melanoma
LOX IMVI -5.07 -4.18 > -4.00
MALME-3M -4.67 -4.08 > -4.00
M14 -4.93 > -4.00 > -4.00
SK-MEL-2 -4.71 -4.06 > -4.00
SK-MEL-28 -4.37 > -4.00 > -4.00
SK-MEL-5 -4.90 -4.46 -4.02
UACC-257 -4.85 > -4.00 > -4.00
UACC-62 -4.90 -4.20 > -4.00
Ovarian Cancer
IGROV1 -4.58 > -4.00 > -4.00
OVCAR-3 -5.21 -4.42 > -4.00
OVCAR-4 -5.17 > -4.00 > -4.00
OVCAR-5 > -4.00 > -4.00 > -4.00
OVCAR-8 -4.84 > -4.00 > -4.00
SK-OV-3 -4.35 > -4.00 > -4.00
Renal Cancer
786-0 -5.01 -4.15 > -4.00
A498 -4.94 -4.34 > -4.00
ACHN -4.95 -4.05 > -4.00
CAKI-1 -4.72 > -4.00 > -4.00
RXF 393 -5.45 -4.75 > -4.00
SN12C -5.67 -5.27 -4.71
TK-10 -4.79 > -4.00 > -4.00
UO-31 -4.60 > -4.00 > -4.00
Prostate Cancer
PC-3 -5.33 -4.18 > -4.00
DU-145 -4.41 > -4.00 > -4.00
Breast Cancer
MCF7 -5.38 -4.58 > -4.00
NCI/ADR-RES -5.09 > -4.00 > -4.00
HS 578T -4.42 > -4.00 > -4.00
MDA-MB-435 -4.85 > -4.00 > -4.00
MDA-N -5.09 > -4.00 > -4.00
BT-549 -4.30 > -4.00 > -4.00
T-47D -5.37 > -4.00 > -4.00
MG_MID -4.92 -4.15 -4.02
Delta 0.75 1.12 0.69
Range 1.57 1.27 0.71
+3 +2 +1 0 -1 -2 -3

FIG. 71

National Cancer Institute Developmental Therapeutics Program
Mean Graphs

NSC: 716407 -M / 1	Units: Molar	SSPL: 0GVG	Exp. ID:0004MD35-16
Report Date: May 22, 2000		Test Date:	

Panel/Cell Line	Log_{10} GI50	Log_{10} TGI	Log_{10} LC50
Leukemia			
CCRF-CEM	-4.43	> -4.00	> -4.00
HL-60(TB)	-4.60	-4.19	> -4.00
K-562	-4.49	> -4.00	> -4.00
MOLT-4	-4.47	> -4.00	> -4.00
RPMI-8226	-4.57	-4.15	> -4.00
SR	-4.56	-4.13	> -4.00
Non-Small Cell Lung Cancer			
A549/ATCC	-4.42	> -4.00	> -4.00
EKVX	-4.52	-4.13	> -4.00
HOP-62	-4.44	-4.04	> -4.00
HOP-92	-4.58	-4.19	> -4.00
NCI-H226	-4.50	-4.01	> -4.00
NCI-H23	-4.53	-4.06	> -4.00
NCI-H322M	-4.44	> -4.00	> -4.00
NCI-H460	-4.52	> -4.00	> -4.00
NCI-H522	-4.60	-4.16	> -4.00
Colon Cancer			
COLO 205	-4.73	-4.46	-4.18
HCC-2998	-4.34	> -4.00	> -4.00
HCT-116	-4.50	> -4.00	> -4.00
HCT-15	-4.48	> -4.00	> -4.00
HT29	-4.45	> -4.00	> -4.00
KM12	-4.51	> -4.00	> -4.00
SW-620	-4.39	> -4.00	> -4.00
CNS Cancer			
SF-268	-4.43	> -4.00	> -4.00
SF-295	-4.47	-4.04	> -4.00
SF-539	-4.67	> -4.00	> -4.00
SNB-19	-4.34	> -4.00	> -4.00
SNB-75	-4.53	-4.09	> -4.00
U251	-4.40	> -4.00	> -4.00
Melanoma			
LOX IMVI	-4.55	-4.11	> -4.00
MALME-3M	-4.59	-4.10	> -4.00
M14	-4.43	> -4.00	> -4.00
SK-MEL-2	-4.62	-4.30	> -4.00
SK-MEL-28	-4.29	> -4.00	> -4.00
SK-MEL-5	-4.49	-4.06	> -4.00
UACC-257	-4.53	> -4.00	> -4.00
UACC-62	-4.52	> -4.00	> -4.00
Ovarian Cancer			
IGROV1	-4.45	> -4.00	> -4.00
OVCAR-3	-4.47	-4.09	> -4.00
OVCAR-4	-4.50	> -4.00	> -4.00
OVCAR-5	-4.61	-4.21	> -4.00
OVCAR-8	-4.43	> -4.00	> -4.00
SK-OV-3	-4.44	-4.04	> -4.00
Renal Cancer			
786-0	-4.47	> -4.00	> -4.00
A498	-4.59	-4.16	> -4.00
ACHN	-4.57	-4.21	> -4.00
CAKI-1	-4.56	> -4.00	> -4.00
RXF 393	-4.61	-4.18	> -4.00
SN12C	-4.60	> -4.00	> -4.00
TK-10	-4.42	> -4.00	> -4.00
UO-31	-4.48	> -4.00	> -4.00
Prostate Cancer			
PC-3	-4.46	> -4.00	> -4.00
DU-145	-4.35	> -4.00	> -4.00
Breast Cancer			
MCF7	-4.55	-4.05	> -4.00
NCI/ADR-RES	-4.47	-4.07	> -4.00
HS 578T	-4.32	> -4.00	> -4.00
MDA-MB-435	-4.56	-4.04	> -4.00
MDA-N	-4.54	> -4.00	> -4.00
BT-549	-4.25	> -4.00	> -4.00
T-47D	-4.49	-4.05	> -4.00
MG_MID	-4.49	-4.05	-4.00
Delta	0.24	0.40	0.18
Range	0.49	0.46	0.18

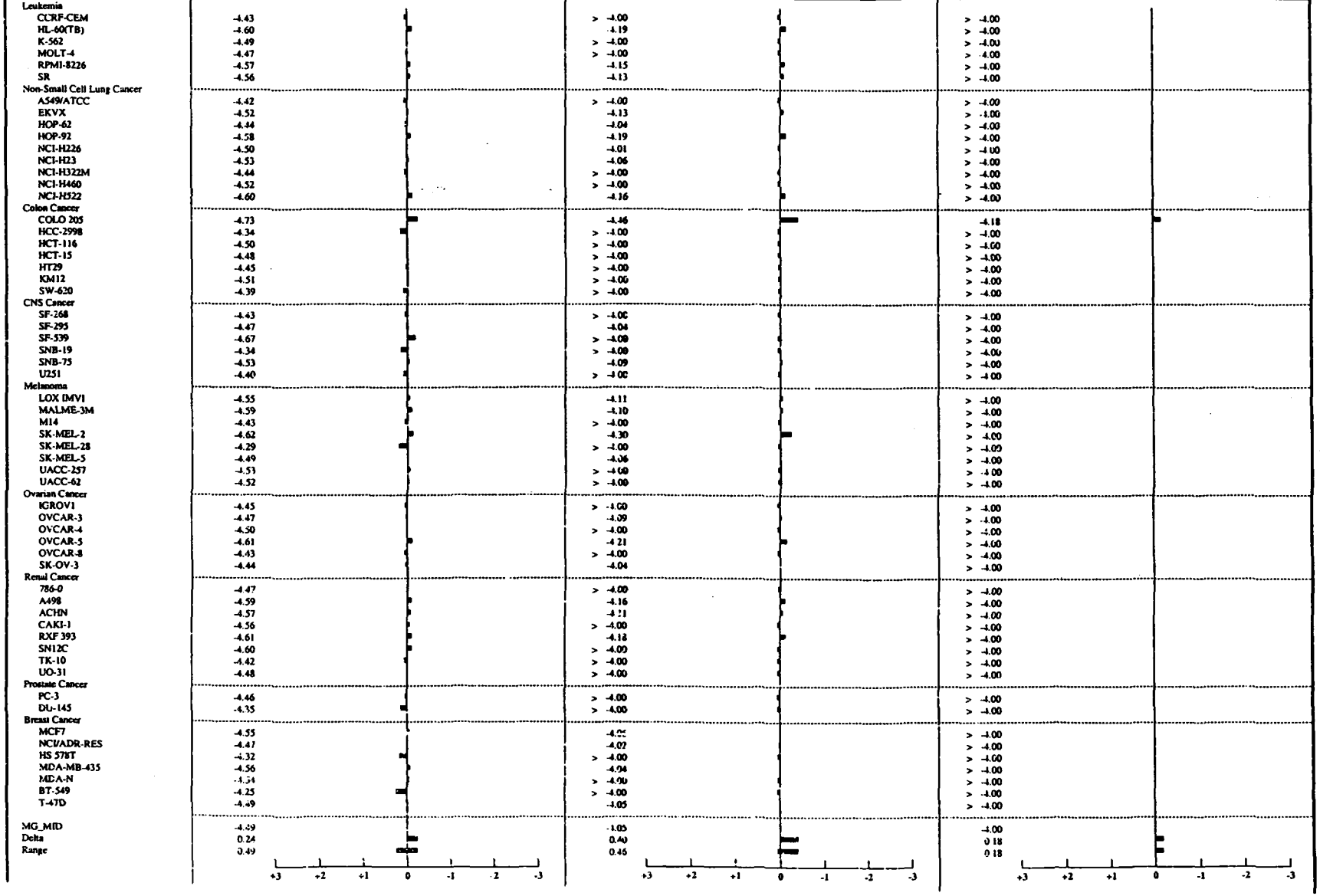

FIG. 72

(B). ANTIBACTERIAL ACTIVITY

INTRODUCTION

The test organism used in the study included *Escherichia coli* UP2566 (Central Drug Research Institute, Lucknow, India), *Bacillus subtilis* MTCC-121 (Institute of Microbial Technology, Chandigarh, India) and clinical isolates of *Streptococcus viridans* and *Staphylococcus epidermatis* (Department of Microbiology, J.N. Medical College, AMU, Aligarh, India).

Culture Media and Inoculum

Sabour and Dextrose (SD), Nutrient broth and agar were obtained from Hi-Media Pvt. Ltd. (Bombay, India) and were used for test bacteria. Freshly grown microbial cultures at 37° C were appropriately diluted in sterile normal saline solution to obtain a cell suspension of 10^6 CFU/ml.

Antibacterial assay

Each synthetic compound was dissolved in DMSO to obtain a stock solution of different concentrations ranging from 2000-5000 μg/ml. The agar well diffusion method (Perez *et al.*[3]) as adopted by Ahmad and Arina[4] was used for our assay. 0.1 ml of the diluted inoculum (10^6 CFU/ml) of test organism was spread on NA/SDA (Nutrient Agar/Sabur and Dextrose Agar) plates. Wells of 8 mm diameter were punctured into the agar medium and filled with 100 μl of compound, solvent blank and an antibiotic (chloramphenicol, 100 μg/ml) to which the test bacteria were sensitive. The plates were incubated for 18 h at 37 °C. Antibacterial activity was evaluated by measuring the zone of inhibition against the test organism.

RESULT AND DISCUSSION

A total of 5 compounds were tested against three Gram +ve bacteria (*Streptococcus viridans*, *Staphylococcus epidermatis*, *Bacillus subtilis*) and one Gram -ve bacteria (*Escherichia coli*). The varying level of anti-bacterial activity was detected against one or more test organisms.

Antibacterial activity of test compounds

The results for the antibacterial study of the tested compounds detected against the test organisms *Escherichia coli, Bacillus subtilis, Staphylococcus epidermatis, Streptococcus viridans* are depicted in **TABLE 26.** Solvent control (DMSO) showed non-significant inhibition to test microorganisms.

All the five compounds demonstrated activity against both Gram +ve and Gram -ve bacteria. The compounds exhibited antibacterial activity in the concentration range 200 μg to 400 μg/100 μl. Overall broad spectrum antibacterial activity i.e. active against Gram +ve and Gram -ve was deduced in five compounds. These compounds may be directly explored in the preparation of topical antiinfective agents. However, further exploration requires detailed study on exact MIC values and least toxicity to host cell and system.

TABLE - 28 : Antibacterial Activity of the Compounds

Compounds	Antibacterial activity in terms of zone of inhibition in mm											
	E. coli Effective conc. µg/well			*S. viridans* Effective conc. µg/well			*S. epidermatis* Effective conc. µg/well			*B. subtilis* Effective conc. µg/well		
	200	300	400	200	300	400	200	300	400	200	300	400
$SD_5(12)$	+++	+++	+++	++++	++++	++++	+	+	+	–	–	+
$ClFD_{1C}(10)$	++	++++	++++	++++	++++	++++	+	+	+	+	+	+++
$SD_{7A}(24)$	++++	++++	++++	++++	++++	++++	+++	+++	+++	+++	+++	++++
$SD_{1A}(19)$	+	+	+	+++	++++	++++	–	–	+	–	+	+
$E_{1A}(3)$	+	++++	++++	+	+++	++++	–	+++	++++	+++	++++	++++
Chloramphenicol	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++

Inhibition zone diameter in mm : (-)5, (+)5-10,(++)10-18, (+++)18-24, (++++) 24-30mm

E.coli = *Escherichia coli*; S.V.= *Streptococcus viridans*, SE = *Staphylococcus epidermatis*, B.S.= *Bacillus sublitis*

References

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2. A. Monks, D. Scudiero, P. Skehan, R. Shoemaker, K. Paull, D. Vistica, C. Hose, J. Langley, P.Cronise and A. Vaigro-wolff, *J. Natl., Cancer Inst.*, 1991, **38**, 757.

3. C. Perez, M. Pauli and P. Bazerque, *Acta Biologiae et Medicinae Experimentalis*, 1990, **15**, 113.

4. Arina Z. Beg and I. Ahmad, *World J. Microbiol. and Biotech.*, 2000, **16**, 841.

LIST OF PUBLICATIONS & PRESENTATIONS

1. Bifunctional derivatives of *p,p'*-dichlorochalcone Part III. Synthesis and study for cytotoxic activity of a new compound, 2-[2,2-bis(4-chlorophenyl)ethyl]-2-(4-chlorophenyl)-thiazolidin-4-one from *p,p'*-dichlorochalcone, *Eur. J. Med. Chem.* **37** (2002) 63-67.

2. Synthesis and biological activity of some novel 3,5-disubstituted-2-pyrazolinyl thiocarboxamides from 1,5-bis(aryl)pent-1-,4-dien-3-ones, *Eur. J. Med. Chem.* (2003) (Communicated).

3. Synthesis and biological activity of 2-[3,5-di-aryl substituted-2-pyrazolinyl]-thiazolin-4-one from chalcones. *Indian J. Chem.* (2002) (Communicated).

4. Flavonol glycosides from *Mallotus philipensis* (Euporiaceae), (33rd Annual convention of chemists, Coimbatore, December 26-29, 1996).

5. Synthesis of 2-*p*-chlorophenyl-2-(1'-phenyl-1'-thiapropionic acid ethyl) tetra-hydro-1,3-thiazin-4-one from chalcone. (33rd Annual convention of chemists, Coimbatore, December 26-29, 1996).

ERRATA

Page	Line	For	Read
66	22	doublets	double doublets
123	03	isoquiolines	isoquinolines
204	21	doublets	double doublets
219	07	thiosemicarazone	thiosemicarbazone
225	19	dessolved	dissolved
253	12	insect	insects
254	26	analogs	analogues